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VOL.
7
1958

Announcements

SYMPOSIUM ON CANCER

GUEST EDITORS, SIR ALEXANDER HADDOW, DR. J. R. HELLER, AND DR. SIDNEY FARBER

To appear in the July issue of the JOURNAL OF CHRONIC DISEASES

CONTENTS

Introductory Statement to the Symposium on Cancer.

The Natural History of Cancer. Dr. Leslie Foulds, Royal Cancer Hospital, London, England.

On the Etiology of Cancer. Dr. Michael B. Shimkin, National Cancer Institute, Bethesda, Md.

An Appraisal of Tumor-Virus Problems. Dr. Jacob Furth and Dr. Donald Metcalf, Children's Cancer Research Foundation, Boston, Mass.

A Critical Analysis of "Tumor Immunity." Dr. Morris K. Barrett, National Cancer Institute, Bethesda, Md.

Recent Studies on Pathophysiologic Mechanisms in Human Neoplastic Disease. Dr. Alfred Gellhorn, College of Physicians and Surgeons, University of Columbia, New York, N. Y.

Some Aspects of Virus-Induced Tumors. Dr. R. J. C. Harris, Institute of Cancer Research, London, England.

Radiation-Induced Leukemia in Man, With Particular Reference to the Dose-Response Relationship. Dr. W. M. Court-Brown, Medical Research Council, Western General Hospital, Edinburgh, Scotland.

The National Cancer Chemotherapy Program. Dr. K. M. Endicott, National Cancer Institute, Bethesda, Md.

Clinical Investigations in Cancer Chemotherapy. Dr. Charles G. Zubrod, National Cancer Institute, Bethesda, Md.

Reflections From Cancer Chemotherapy Screening Studies. Dr. C. Chester Stock, Sloan-Kettering Institute, New York, N. Y.

The Immunologic Theory of Cancer: Some Implications in Human Pathology. Dr. H. N. Green, Director of Cancer Research, School of Medicine, University of Leeds, Leeds, England.

SYMPOSIUM ON CHRONIC CONGESTIVE HEART FAILURE

GUEST EDITOR, DR. ALFRED P. FISHMAN

To appear in an early, 1959, issue of the JOURNAL OF CHRONIC DISEASES

TENTATIVE CONTENTS

Pharmacology of the Failing Heart. Dr. John McMichael, Postgraduate Medical School of London, London, England.

Volume Receptors. Dr. Maurice B. Strauss and Dr. Solomon Papper, Veterans Administration Hospital, Boston, Mass.

Myocardial Metabolism in Congestive Heart Failure. Dr. Robert E. Olson, University of Pittsburgh, Pittsburgh, Pa.

The Lung in Congestive Heart Failure. Dr. Alfred P. Fishman and Dr. Gerard M. Turino, Columbia University, New York, N. Y.

Determinants of Venous Pressure. Dr. Arthur C. Guyton, University of Mississippi, School of Medicine, Jackson, Miss.

Physiologic Basis of the Therapy of Pulmonary Edema. Dr. Domingo M. Aviado, Jr. and Dr. Carl F. Schmidt, University of Pennsylvania, School of Medicine, Philadelphia, Pa.

Nutritional Heart Disease. Dr. Chester S. Keefer, Massachusetts Memorial Hospital, Boston, Mass.

Pathology of Congestive Heart Failure. Dr. Marvin Kuschner, New York University, College of Medicine, Bellevue Hospital, New York, N. Y.

Endocrine Factors. Dr. H. P. Wolff, I. Med. Klinik d. Universität, Munich, Germany.

Congestive Heart Failure in Children. Dr. Sidney Blumenthal and Dr. Dorothy H. Andersen, Columbia University, New York, N. Y.

The Kidney in Chronic Congestive Heart Failure. Dr. A. Clifford Barger, Harvard Medical School, Boston, Mass.

Hemodynamics. Dr. Kenneth W. Donald, Queen Elizabeth Hospital, Birmingham, England.

Autonomic Nervous System in the Pulmonary Hypertension of Congestive Heart Failure. Dr. D. Halmagyi, University Medical School, Szeged, Hungary.

VOL
7
195

VOL.
7
1958

Original Communications

ALKAPTONURIA. REPORT OF A FAMILY WITH SEVEN CASES APPEARING IN FOUR SUCCESSIVE GENERATIONS, WITH METABOLIC STUDIES IN ONE PATIENT

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ALKAPTONURIA is an uncommon disorder of metabolism. In addition to presenting interesting clinical aspects, it has received considerable attention from biochemical investigators because of the light its study has shed on the intermediary metabolism of the aromatic amino acids.

The breakdown of phenylalanine and tyrosine occurs in many steps. Disturbances at various sites along their metabolic pathway are known to occur in man and to give rise to several "inborn errors of metabolism." Alkaptonuria was the first of these to be described; less than 250 cases have been reported to date.

The purpose of this paper is to review briefly present knowledge of the disease and to report 8 additional cases, 7 from one family, in one of whom metabolic studies were performed.

HISTORICAL

Garrod[1] in his book *Inborn Errors of Metabolism* has reviewed the early knowledge about this disease. Although cases passing black urine were recorded in the sixteenth and seventeenth centuries, the first accurate description of alkaptonuria came from Boedeker[2] in 1858. He found in the urine of a patient with glycosuria a nonsugar reducing substance which turned black upon addition of alkali. He named this alkapton, a composite word meaning to devour (oxygen) in alkali. In 1891, Wolkow and Baumann[3] identified the alkapton body as homogentisic acid. Virchow,[4] while performing a routine autopsy in 1866,

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noticed an intense brownish pigmentation of all cartilages, ligaments, and tendons, and of the pericardium, periosteum, and media of the large vessels. This pigment appeared brownish-yellow, and Virchow proposed to name the condition ochronosis. Albrecht,[5] in 1902, called attention to the association of ochronosis and alkaptonuria. In 1904, Osler[6] reported the first living case with ochronosis, alkaptonuria, and rheumatic pains.

PREVALENCE

The condition is rare since fewer than 250 cases have been reported in the world literature in spite of the recognition of the condition since the nineteenth century. Only 12 cases were seen at the Mayo Clinic over a 25-year period.[7] No previous cases of alkaptonuria were found among the records of the American University Hospital, numbering nearly 100,000 admissions. The exact incidence of the disease is not yet known since no studies on population surveys have thus far been published.

INHERITANCE

There has been a certain amount of controversy regarding the mode of inheritance of alkaptonuria. From the study of cases available to him, Garrod concluded that the inheritance obeyed the simple Mendelian recessive pattern. Hall, Hawkins, and Child[9] reported 300 relatives with 15 cases of alkaptonuria in which the inheritance was typically recessive. In 1932, Hogben, Worrall, and Zieve[8] reviewed the 44 pedigrees reported up to that date. Thirty-nine of these consisted of alkaptonuric children born to nonaffected parents and therefore conformed to the recessive pattern. In the other 5 pedigrees there was direct transmission of the trait from parent to child. One of these was the pedigree of Pieter[10] where the disease was transmitted from parent to child in four successive generations. Hogben, Worrall, and Zieve took this as evidence for a rarer type of alkaptonuria in which the disease was transmitted as a dominant trait. Once the existence of the dominant form was accepted the remaining four pedigrees could also be fitted into this pattern. However, Pieter made no mention of presence or absence of consanguinity in his pedigree, and one wonders if there had been no intermarriage in this family living on a small island. It is noteworthy that of the 5 alkaptonuric persons in the third generation of Pieter's pedigree only one had affected children while the other 4 were all married and had normal children.

In 1955, Milch[12] reviewed three families and came to the conclusion that the "metabolic disorder is determined by an incompletely penetrant dominant gene substitution which coexists with at least one other pair of modifying factors." This interpretation was based on two instances of direct transmission of the disease. The fact that marriage between an alkaptonuric and a normal nonrelated person produces an alkaptonuric child cannot be taken as an argument against the recessive form of transmission on the assumption that since the disease is very rare, it is statistically unlikely that the nonaffected parents were heterozygotes. Statistical analysis cannot be applied to this study since

the incidence of the disease is unknown. Moreover, families in which the disease appears in more than one generation are much more likely to be detected and to be reported.

It thus appears that although an alternate form of inheritance cannot be excluded the available data are consistent with a Mendelian recessive pattern of inheritance.

CHEMICAL PATHOLOGY

The chemical pathology of alkaptonuria has been extensively investigated.[13-23] Fig. 1 outlines the metabolic pathway of phenylalanine and tyrosine. Homogentisic acid is an intermediary product in the breakdown of these amino acids and is itself oxidized by the action of the enzyme homogentisicase to maleylacetoacetic acid[24] which is converted to fumarylacetoacetic acid and finally to fumaric and acetoacetic acid. The enzyme has been found in liver, kidney, and bacteria. It requires ferrous iron. Ascorbic acid and glutathione activate the system nonspecifically. Homogentisic acid excretion can be produced by feeding large doses of tyrosine and phenylalanine to guinea pigs and rats.

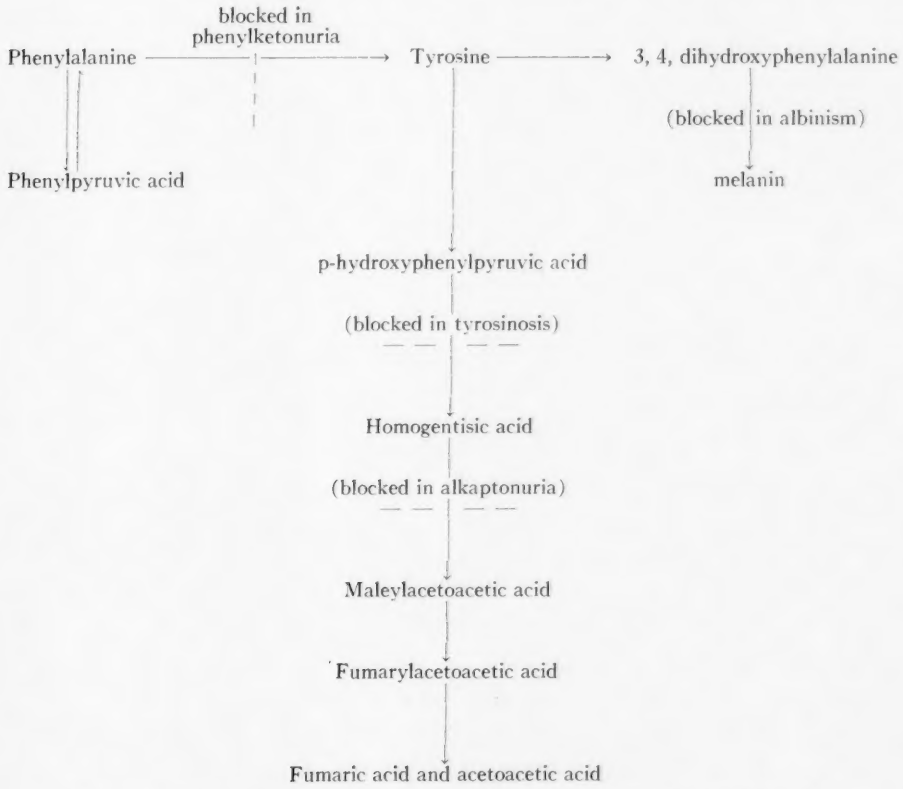

Fig. 1.—Outline of phenylalanine and tyrosine metabolism, indicating sites of block in different diseases.[13,14,24,25]

Human alkaptonuria is due to a hereditary defect in the homogentisicase system. Thus homogentisic acid breakdown is depressed, resulting in accumulation of the metabolite in the blood and excretion in the urine. An oxidized polymer of homogentisic acid is deposited in tissues giving rise to ochronosis. The relation between pigment deposition in the cartilages and the pathogenesis of arthritis is not elucidated. Attempts to correct the metabolic defect by the administration of substances that could possibly act as cofactors have so far failed. Whether the block is complete or partial has not yet been conclusively ascertained, but present evidence favors a complete block. On a regular diet alkaptonuric patients excrete 50 to 85 per cent of the ingested phenylalanine and tyrosine as homogentisic acid. The remainder has not been accounted for. Oxidized homogentisic acid and phenylacetylglutamine which is found in normal urine[26] account for part of the balance.

The administration of extra phenylalanine and tyrosine to human alkaptonurics results in their almost quantitative excretion as homogentisic acid.[16,18] Seegmiller, LaDu, Zanoni, and Laster[27] have found no homogentisicase activity in the liver of a patient with alkaptonuria.

CLINICAL PICTURE

The Urine.—The earliest abnormality to be noticed is the black staining of the diapers. The urine may be normal in color on voiding but turns black upon exposure to air. This blackening occurs much faster if the urine is alkaline.

Skin and Cartilages.—The deposition of pigment in the skin and cartilages produces a peculiar greenish-brown discoloration which was named ochronosis. The pigmentation is light and patchy during the first decades of life, tending to become darker and more diffuse with advancing age. It is most conspicuous on the ear cartilages, face, and in the axillae. The pigment is also found in the cerumen and the sweat.

Ochronosis should be differentiated from other diseases associated with pigmentation such as hemochromatosis, Addison's disease, chronic hepatic disease, argyrosis, porphyria, and atabrine poisoning,[28,29] and that following prolonged external use of phenol.[30,49]

The Eyes.—Most authors have reported[11,18,31-37] ocular changes in alkaptonuria. In general these appear earlier than the skin changes and like the latter are variable in intensity but progressive. Pigmentation usually starts as a patch over the sclera at the palpebral fissure. The pigmented area may be striped, triangular, or circular in shape, and is of variable size. It may be brownish-blue or black. Similar pigmentation may occur in phenol poisoning and in the course of lengthy exposure to the vapors and dust of quinone.

The cornea is also involved and slit-lamp examination reveals fine pigment granules in the superficial layers near both limbi. This finding is considered diagnostic by Smith.[11] It is important to recognize scleral ochronosis in order to differentiate it from more serious conditions such as melanosarcoma.[33]

Smith[11] has published a comprehensive review of the eye changes in alkaptonuria.

VOL 7 195

The Joints.—Among the manifestations of alkaptonuria, arthritis is the most disabling and bothersome to the patient. This aspect of the disorder has been the subject of numerous reports.[11,18,31,32,35,38-48]

The average age at which arthritis becomes manifest is about 50 years; its course is progressive. The patient first notices rigidity and pain in the spinal column which increases in severity. Thoracic kyphosis develops while the lumbar curvature may increase or decrease. Pain and limitation of motion also occur in the hips, knees, and shoulders. In advanced cases the hip and knee joints are flexed, and the patient stands on a wide base. Occasionally the gait is waddling. In general, the small joints are spared; only a few reports mention their involvement.[39,42] The condition is chronic and slowly progressive. Acute exacerbations with synovial effusion may occur according to Hench.[38] Sutro and Anderson report the occurrence of free intra-articular bodies.[45] Clinical differentiation from degenerative arthritis can be made if the condition is kept in mind and by the fact that in alkaptonuric arthritis nonweight-bearing joints are also affected.

The radiologic findings in the spine are almost pathognomonic.[35,46,48] There is marked thinning and dense calcification of the intervertebral disks which look elliptical and waferlike. They may be extruded or resorbed causing fusion of vertebral bodies. This process may be accompanied by exostosis and ligamentous calcification. The sacroiliac joints are narrowed but not calcified. Calcification of the interpubic disk may be seen. The lumbosacral and hip joints show findings similar to osteoarthritis.

The shoulder joints are narrowed. There may be flattening of the head of the humerus suggestive of neuropathic arthritis, and ankylosis of the joint occurs in advanced cases. The small joints show only periarticular swelling. Calcification may occur in the tendons, ligaments, and bursae and in synovial membranes around large joints.

Cardiovascular System.—Various authors[18,31,34,42,49] have stressed the association of alkaptonuria with degenerative and valvular lesions of the heart. Further studies are needed to ascertain if an etiologic relationship exists between alkaptonuria and heart disease.

Genitourinary System: Prostatic concretions of ochronotic pigment are reported in elderly patients and may be a cause of dysuria.[32,42,50] Since such concretions may be passed in the urine, the presence of black calculi should suggest ochronosis. Renal[50] and ureteral[51] stones have also been reported.

PATHOLOGY

At autopsy pigmentation is found to be most intense in tendons, cartilages, and calcified and atheromatous regions which may appear completely black. The internal organs and the meninges may show patches of gray-black pigment.[18]

Histologically, the pigment appears light brown or yellow, either homogeneous or granular. Pigment deposition also occurs intracellularly and in severe cases obliterates the cell architecture. The pigment does not take iron or fat stains. It stains black with polychrome blue but does not increase in intensity when stained with silver nitrate.[52]

LABORATORY FINDINGS

No abnormalities have been reported in the routine hematologic and biochemical examinations of the blood.

Numerous tests have been described for the detection of homogentisic acid in the urine.[44] The urine turns dark upon exposure to air; blackening occurring within minutes if a few drops of sodium hydroxide are added and the urine shaken. It reduces copper solutions (Benedict's and Fehling's) but does not reduce alkaline bismuth solution. Addition of dilute ferric chloride to the urine gives a transient blue color. Addition of Millon's reagent gives a yellow precipitate while a deep blue color develops upon addition of Folin-Ciocalteu phenol reagent. When alkalinized urine is dropped over sensitized photographic paper, a black color develops.[53] The definitive diagnosis of alkaptonuria depends on the isolation of crystalline homogentisic acid from urine and its identification by melting point determination.

TREATMENT

Attempts to correct the metabolic defect by the administration of vitamins, hormones, and other drugs have so far failed.[18,32,34,41,54,55] Therapy remains symptomatic and directed toward the relief of arthritic pains.

In view of the evidence in favor of a recessive mode of transmission of the disease, intermarriage in alkaptonuric families should be discouraged.

CASE REPORTS

CASE 4 (AUH No. 113826).—A 54-year-old Arab man was admitted to the hospital because of pain and limitation of movement of 6 years' duration, involving the spine, hips, knees, and shoulders. Pain was more severe on awakening and was partially relieved by mild exercise and by application of heat. For the past 5 years he had been complaining of difficulty in starting urination and of interruption of the stream of urine. For as long as he could remember he had noticed that his urine turned dark on standing and his underwear stained black.

On examination the positive findings included a rather dark skin with brown patches of pigment on both sides of the cornea bilaterally. The pinnae were violaceous; on the margin of the right pinna there were numerous small hard nodules with black centers. The prostate was large, nodular, and small stony hard masses were felt within it. One of these was crushed by massage and the patient passed immediately black sandlike material in the urine. There was limitation of motion of the spine and shoulders. The remainder of the examination was negative.

Laboratory examinations including red blood count, white blood count, hemoglobin, hematocrit, blood urea, sugar, serum sodium, potassium, chloride, carbon dioxide combining power, total protein, albumin-globulin ratio, alkaline and acid phosphatases, bilirubin, nonprotein nitrogen, and creatinine were all within normal limits. Phenolsulfonphthalein excretion was 20 per cent in 2 hours. The urine was positive for homogentisic acid by the ferric chloride, Millon's phenol and sensitized photographic paper tests. Homogentisic acid was crystallized from the urine and had a melting point of 144° to 145°C. The sediment of the urine contained numerous white blood cells.

On radiologic examination the intervertebral disk spaces in the dorsal and lumbar spine were markedly narrowed. The flattened disks showed uniform calcification. There was relatively little osteoarthritic lipping. The joint spaces of the shoulders were narrowed, and there was osteoarthritic deformity of the glenoid fossae. The hands showed no lesions; roentgenogram of the chest and electrocardiogram were normal. An intravenous pyelogram was normal.

The patient volunteered the information that his mother, both grandmothers, and three of his children were passing black urine. We therefore undertook a trip to the village where members of his family have been living for many generations and interviewed all the available members of his large family. The passage of black urine was regarded as an amusing curiosity by these peas-

ants and was a well-known fact to all members of the family, young and old. The history of the deceased persons was confirmed from numerous sources by three different historians and can therefore be considered reliable.

The pedigree in Fig. 3 shows the distribution of the disease. All the living members included in this chart were interviewed, and the urine was tested for homogentisic acid.

Fig. 2.—Roentgenogram of the thoracic spine.

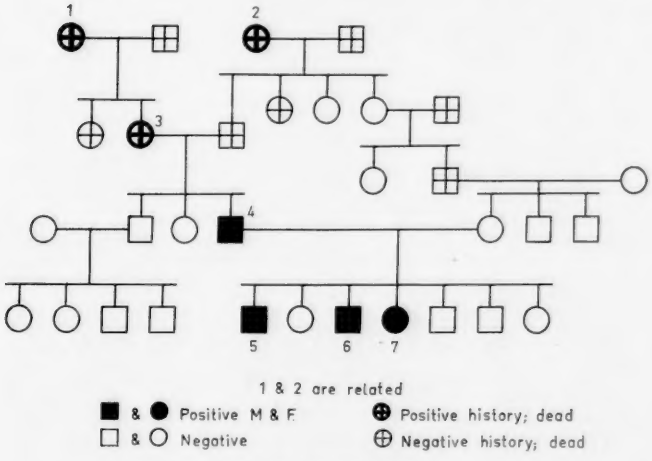

Fig. 3.—Family tree.

CASES 1, 2, and 3.—The two grandmothers (first cousins) and the mother of Patient 4 were deceased. There was a history of passage of black urine confirmed from several sources.

CASE 5.—The 20-year-old son of Patient 4 had passed black urine since birth and for the last two years had stiffness of the back. Physical examination revealed ochronotic pigmentation and mild limitation of movement at the lumbar vertebrae. A roentgenogram of the spine was negative. Homogentisic acid was demonstrated in the urine.

CASES 6 and 7.—A 13-year-old daughter and a 1-year-old son of Patient 4 both passed black urine. Systemic inquiry and physical examination were negative. Urine of both was positive for homogentisic acid.

CASE 8.—A 9-month-old male infant passed black urine in which homogentisic acid was demonstrated. Physical examination was negative. The father and mother were not related to each other nor to the family above and came from a different town in Lebanon. The urine of both was negative for homogentisic acid. They have no other children and there is no family history of passage of black urine.

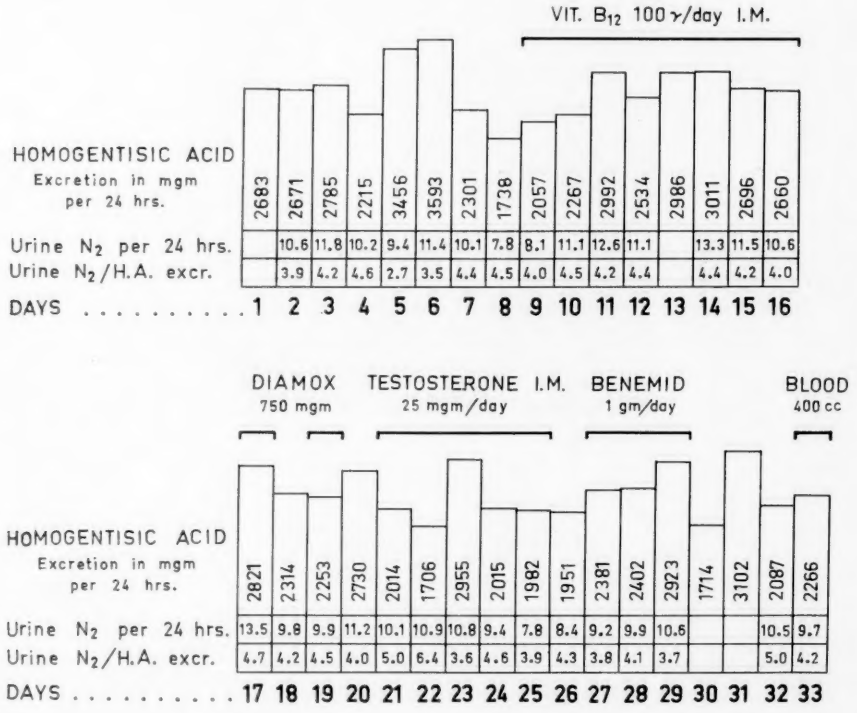

Fig. 4.—Daily excretion of nitrogen and homogentisic acid during the control period and during administration of various substances.

STUDIES

Patient 4 was hospitalized and the following studies were carried out. The patient was maintained on a diet of proteins 80 Gm., carbohydrates 250 Gm., fat 70 Gm. prepared by the hospital kitchen. Twenty-four hour urine specimens were collected in dark, stoppered bottles containing 100 c.c. of N HCl.

Homogentisic acid was determined in the urine by the method of Briggs[56] as modified by Neuberger.[15] All determinations were done in duplicate. Total nitrogen in the 24-hour sample of urine was determined by digestion and nesslerization.

After a control period of 8 days the following substances were administered, and their effect on the 24-hour urinary homogentisic acid excretion was measured.

1. Vitamin B_{12}, 100 mg. per day administered intramuscularly daily for 8 days.
2. Methyltestosterone 25 mg. per day intramuscularly for 5 consecutive days.
3. Acetazoleamide (Diamox) 750 mg. by mouth in the morning, two doses at 48-hour intervals.
4. Probenecid (Benemid) 1 Gm. per day by mouth for 3 consecutive days.
5. One transfusion of 400 ml. of fresh whole blood.

Results are shown in Fig. 4.

During the control period the homogentisic acid excretion varied between 1,738 and 3,593 mg. per day. On a diet of 60 Gm. of protein per day the patient was ingesting an average of 6 Gm. of phenylalanine plus tyrosine per day, equivalent to 5.8 Gm. of homogentisic acid. He was then excreting only 46 per cent of the ingested precursors as homogentisic acid. This is definitely lower than the conversion ratio of 85 per cent found by Neuberger,[7] but cannot be taken as evidence for a partial block in this patient. No studies were done to account for the balance.

The various substances administered did not affect significantly the excretion of homogentisic acid.

DISCUSSION

The vast majority of reported pedigrees conform to the Mendelian recessive pattern. Direct inheritance appears in ten families.[8,10,11,12] In many of these there is no information regarding possible intermarriage. Therefore, the available data are inadequate to substantiate the claim for an alternate, dominant form of alkaptonuria. The pedigree reported above conforms to the recessive pattern in spite of the appearance of the disease in four successive generations.

SUMMARY

The literature on alkaptonuria is briefly reviewed. A family with seven alkaptonurics appearing in four successive generations is presented. The inheritance in this family conforms to the Mendelian recessive pattern.

Administration of vitamin B_{12}, methyltestosterone, acetazolamide, probenecid, and fresh whole blood did not alter significantly the 24-hour urinary excretion of homogentisic acid.

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VOL. 7 1958

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VOL.
7
1958

PSYCHOSOCIAL FACTORS IN THE EPIDEMIOLOGY OF RHEUMATOID ARTHRITIS

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VOL
7
195

IT HAS long been supposed that psychological and social factors play a role in rheumatoid arthritis. This is largely a matter of clinical impression, for there have been few well-designed and carefully controlled research projects in this area.[5] In particular, there is a noticeable paucity of studies utilizing control groups of individuals with other disease or without any demonstrable disease. In the hope of meeting some of this deficiency, the present report describes an investigation that utilized a population study based on a random sampling procedure, making it possible to compare people with and without rheumatoid arthritis.

PROCEDURE

In 1951 and 1952, a probability sample of households in the Arsenal Health District of Pittsburgh was drawn and interviewed as part of a general health survey.[1,4] From the 7,132 persons over 15 years of age in the household sample, 1,323 were selected for individual interviews during 1953-1954 and from the individual interview 707 persons were later invited for a complete physical examination of whom 478 were actually examined.[2] It is with the group of 1,323 that we are primarily concerned in this paper.

During the individual interview, the respondents were asked a number of questions about arthritic symptoms. As reported by Rubin, Rosenbaum, and Cobb,[9] three of the history questions proved to be an Index of Rheumatoid Arthritis that is useful and appropriate for the study of associations between the disease and environmental factors of interest. This index is defined as a "yes" answer to all three of the following questions: (1) Have you ever had arthritis or rheumatism? (2) Have you ever had swelling in any joints? (3) Do you wake up with stiffness or aching in your joints or muscles?

In studying the 478 respondents who later had a complete physical examination and x-ray studies, it was found that a positive index had a sensitivity of

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0.65 for the diagnosis of rheumatoid arthritis and a specificity of 0.95. These figures mean that the index would show a proportion of 0.05 false positives and 0.35 false negatives, results that compare favorably with those for the early Wassermann test.[6]

Our procedure was to study those respondents with a positive index, comparing them with respondents who had a negative index, using as the basis for comparison data on a number of host and environmental variables which were obtained in the individual interview and the household survey and which appeared on preliminary examination to show differences between the two groups. Some confirmation of the validity of this approach will be considered in the discussion section, for the associations detected by the index were also evident in the smaller, examined group.

VOL.
7
1958

In the sample of 1,323 persons, interviews were obtained from 1,166, of whom 200 were classified as having a positive index and 966 as having a negative index. Inasmuch as the sample was selected on a stratified basis, it was necessary to weight the raw numbers to bring the strata back to the correct proportion in the total sample. In addition, the data were adjusted for age inasmuch as each of the variables under consideration was to some extent dependent on age. In doing this, we followed the indirect method, as described by Linder and Grove,[8] using the total study population of the original health survey as a base. Our comparisons therefore are with appropriately weighted and age-adjusted figures.

Data were tabulated on educational level reached by the respondent, marital status, current family income, number of children in respondent's family, use of leisure time in the third decade of life, and judgment of worries as compared with others. Procedural explanation concerning three of these factors is pertinent at this point. Current family income was obtained by showing the subject a card on which four income groups were listed: less than $1,500 a year, $1,500-$3,000 a year, $3,000-$4,500 a year, and over $4,500 a year. The respondent then indicated the appropriate group for his situation. In the case of leisure activities, replies were obtained to the question: What did you like to do with your spare time when you were in your 20's? The replies were then divided into those who indicated that they had no spare time and those who listed specific activities, whether of an active or inactive nature. Information about worries came from the question: Do you feel that you tend to be more or less worried and nervous than most people? The respondent chose one of three categories for his answer: more, average, or less.

RESULTS

The variables which we studied in detail are listed in Table I. The numbers in the columns following each item represent the percentage of men or women having a positive Index of Rheumatoid Arthritis out of all men or women who could be characterized by that item. For example, of all men reporting a family income of less than $3,000 a year, 7.2 per cent had a positive index, or of all women who had four or more children, 25.4 per cent had a positive index.

TABLE I. PER CENT OF PERSONS WITH CERTAIN SOCIAL CHARACTERISTICS WHO WERE CLASSIFIED AS HAVING A POSITIVE INDEX OF RHEUMATOID ARTHRITIS
(Age-Adjusted Rates Per 100 Persons of Each Sex Who Are 15 Years of Age or Older)

ITEM		MALE	FEMALE
1. Current family income:	less than $3,000 a year	7.2 (22)	7.5 (67)*
	$3,000-$4,499 a year	3.3 (12)	6.2 (35)
	$4,500 or more a year	0.6 (5)	6.8 (27)
2. Highest educational level reached:	less than fifth grade	3.9 (8)	39.1 (33)
	Grades 5-8	1.3 (13)	8.3 (62)
	Grade 9 or higher	3.5 (13)	5.7 (49)
3. Marital status:	Single	0.9 (2)	7.6 (20)
	Married	2.9 (30)	7.4 (80)
	Marriage terminated by death, divorce, or separation	27.3 (9)	7.6 (59)
4. Number of children:	None, or respondent single	1.1 (8)	6.5 (43)
	1 or 2	7.3 (19)	3.3 (37)
	3	0.4 (1)	6.3 (21)
	4 or more	1.3 (10)	25.4 (40)
5. Type of leisure activity in the third decade of life:			
	No spare time	3.0 (8)	9.5 (40)
	Active or inactive	4.2 (29)	7.3 (107)
6. Judgment of worries compared with others:			
	Same or less than others	3.3 (33)	7.3 (85)
	More than others	11.7 (8)	8.8 (68)

*Numbers in parenthesis are the original cases, before weighting and age adjusting.

A number of findings stand out in Table I. Under income, the rate for men with less than $3,000 income is twelve times higher than for men with $4,500 or more. In the second variable, education, the rate for women with less than a fifth grade level is very high, almost 40 per 100. The male rate is in the same direction, but only to a slight degree. Marital status shows a high rate for men who have had a termination of marriage, more than nine times that of married men. Considering number of children, the situation differs for men and women in that the highest rate for men comes with those who have only one or two children, while for women it is with those who have four or more children. Finally, it is to be noted that men who report that they worry more than others have a higher rate than men in the other worry category.

Our next step was to select certain items from the six general variables and study the cumulative effect, that is, to study the differences in prevalence among subjects who did not have any of the items we selected, and subjects who had one or more of the items. In choosing our items we were guided by the extent of difference between the categories in each general variable, and also by the theoretical relevance of an item for inducing stress. Thus, the termination of marriage was selected on both counts, because it had a strikingly different rate for men than the other civil state categories, and also was theoretically relevant as a stress factor. No spare time in the third decade of life was selected pri-

marily because we felt that it had connotations for stress in American culture. The results are presented in Table II.

Considering first the men, the items were: family income less than $3,000 a year, less than a fifth grade education, termination of marriage, worries more than other people, and no spare time in the third decade of life. The difference between the subjects with none of the items and subjects with two or more of them is almost twenty-seven fold, quite a striking finding.

TABLE II. THE RELATIONSHIP BETWEEN CERTAIN SOCIAL FACTORS AND THE PER CENT OF PERSONS CLASSIFIED AS POSITIVE ON THE INDEX OF RHEUMATOID ARTHRITIS
(Age-Adjusted Rates Per 100 Persons of Each Sex Who Are 15 Years of Age or Older)

NUMBER OF FACTORS PRESENT	ADJUSTED RATE PER 100	NUMBER OF CASES
*Relevant Factors for Males**		
None	0.6	10
One	4.4	15
Two or more	15.4	16
Relevant Factors for Females†		
None	2.0	18
One	7.4	46
Two	9.8	48
Three	17.1	27
Four or more	33.3	20

*Income less than $3,000, less than a fifth grade education, marriage terminated, no spare time in the third decade of life, worry more than other people.

†Income less than $3,000, less than a fifth grade education, marriage terminated, four or more children, no spare time in the third decade of life, worry more than other people.

The same items were used for women, plus having four or more children, making six in all. The difference between those women with none of the six and women with four or more items is sixteen fold.

The next step involved consideration of combinations of the items which might produce the same result as the total group of items. For men this search was rather successful, indicating that a family income of less than $3,000 a year, less than a fifth grade education, and termination of marriage produced even more striking differences in prevalence than all five items. The rate per hundred for men with none of the three was 0.8, for one was 8.0, and for two or more was 29.3, a thirty-six fold difference between none of the items and two or more.

Results were not so fortunate for the women. No combination of items gave as striking differences as did the use of all six items. However, when less than a fifth grade education, four or more children, no spare time in the third decade of life, and worries more than others were combined, the prevalence rate for three or more of these items rose to 51.6. The rate for none of the items rose correspondingly, to. 5.1, so that the difference was only tenfold.

While working with the combination of various items, we were struck with the results of the interrelation of income and education, which is presented graphically in Fig. 1. Among all respondents with less than a fifth grade education the prevalence of a positive index was six times as high for those with an income of over $3,000 a year as compared to those with less than $3,000 income. At the other end of the educational scale, ninth grade or better, the prevalence rate was much higher among those with lower income. Thus the rates were relatively larger when education was low and income high, or when education was high and income low.

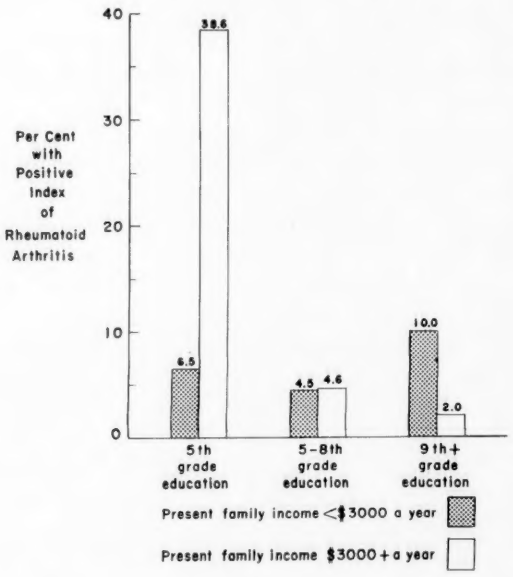

Fig. 1.

Finally, we were interested in pursuing the association of the number of children with the prevalence of a positive index. As shown in Table I, the important items were one or two children for men, but four or more children for women. We were concerned that this result might be affected by the age of the respondents, hence we divided our group into those within the ordinary child-creating age span, 25 to 44 years, and those beyond it, 45+ years. The results are shown graphically in Fig. 2. It will be noted that the pattern is essentially the same in the two age groups.

The association of number of children and a positive index suggested that it would be valuable to study the number of siblings each respondent had. Unfortunately, our data here were limited only to those 478 subjects who were later given a complete physical examination. Hence, our results must be regarded as tentative, even though interesting. In the case of women, those who had four or more children and also had three or more siblings, showed a crude prevalence

rate* of a positive index of 54.6. Among the men, those who had only one child yet came from a family with three or more siblings, showed a crude prevalence of 43.4. In both cases there appeared to be an effect of a large number of siblings, potentiating the factor of many children with women, and few children with men. Unfortunately, the number of cases here is small, but the results are sufficiently striking to indicate their consideration in future research.

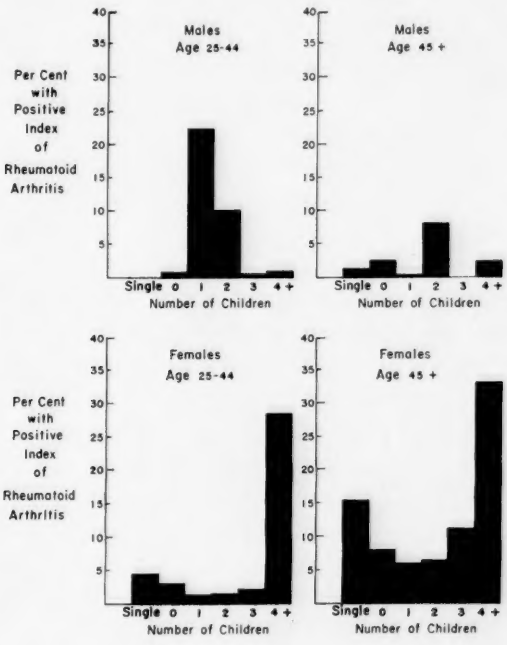

Fig. 2.

DISCUSSION

Using the Index of Rheumatoid Arthritis we have shown that there are interesting differences between individuals with a positive index and those with a negative index. We stated earlier that Rubin, Rosenbaum, and Cobb[9] found the index to be a valid instrument for studying associations between the disease and environmental factors. It is worth noting that our findings and the conclusions of Rubin, Rosenbaum, and Cobb are strengthened when one compares the data, using the index, with the data on the respondents who were classified on the basis of a complete medical examination.

In general, the comparison is more than satisfactory. For example, the cumulative data on males and females, presented in Table II, can be compared with the same factors in subjects who were diagnosed as having probable or definite rheumatoid arthritis (ARA criteria). This is shown in Table III. For

*Because of the small numbers in some of the cells in the tables, we did not compute age-adjusted rates.

VOL.
7
1958

TABLE III. THE RELATIONSHIP BETWEEN CERTAIN SOCIAL FACTORS AND THE PER CENT OF PERSONS DIAGNOSED AS HAVING RHEUMATOID ARTHRITIS
(Age-Adjusted Rates Per 100 Persons)

NUMBER OF FACTORS PRESENT	ADJUSTED RATE PER 100	NUMBER OF CASES
*Relevant Factors for Males**		
None	0.2	2
One	0.2	1
Two or more	1.8	4
Relevant Factors for Females†		
None	2.0	3
One	2.9	6
Two or more	5.4	14

*Income less than $3,000, less than a fifth grade education, marriage terminated, no spare time in third decade of life, and worry more than other people.

†Income less than $3,000, less than a fifth grade education, marriage terminated, four or more children, no spare time in the third decade of life, and worry more than other people.

both sexes the prevalence rate increases as one goes from those respondents with none of the items to those with one, two, or more. Though the numbers are small, they are in the same direction as the results obtained using the Index.

Going one step further, one can compare the rates for the index group and the examined group using the three items for men that appeared to be of most importance—less than fifth grade education, family income less than $3,000 a year, and termination of marriage. In the examined group the rates go from 0.2 for none of the items, to 0.5 for one item, and to 16.7 for two or more items. In both sets of data, the index and the examination, these three items appear to be the most important ones among the five.

Four items out of the six which were used for the women appeared to be important, although we pointed out that the results using these four were not radically different from the results using all six. For the examined women, considering less than fifth grade education, four or more children, no spare time in the third decade of life, and worries more than other people, the rates go from 1.7 for none of the items, to 6.8 for one item, and 5.0 for two or more. Again, the results are in the same direction as one finds when using the index data.

Returning to the three items which were of central importance for men, it seems a reasonable interpretation that indeed these are often stressful in the American culture. Low education and low income place a person at a disadvantage in the prestige scale, or in the ability to obtain many of the material goods deemed so important. Marital separation, for whatever reason, is especially difficult in a society where there are few groups with which one can become identified in a close, personal way and where one must depend on ties in the immediate family for the main source of emotional support. Each of these items could be equally stressful for women.

No spare time during the third decade of life implies a situation where hard work and overburdening responsibilities could conflict with the cultural emphasis on recreation and "having fun," especially during the younger years. This could become doubly stressful for a woman when followed by the problems and cares of rearing a large family. We were originally interested in the observation that patients with rheumatoid arthritis give a history of excessive activity,[5] and actually had rather expected to see this expressed in terms of very active recreation rather than as a lack of spare time. Finally, for both sexes, subjective evaluation of worries as greater than other people might point to inadequate personality resources for meeting the demands of everyday living.

One factor from those used in Tables II and III merits further comment, that of marital status. In his study for the Empire Rheumatism Council, Lewis-Faning[7] showed that married men for all age groups had higher attack rates for rheumatoid arthritis than did single men. The association was strongest in the age group of 15 to 34 years. Using a positive Index of Rheumatoid Arthritis as a measure, our data support Lewis-Faning's results. Married men at all ages have a higher risk, the most vulnerable age group being that of 15 to 34 years. Lewis-Faning did not emphasize, however, the importance of termination of marriage in the civil state categories. We were able to do this in our data, and thus extend the gradient, showing that the risk for males is lowest in the single group, greater in the married group, but greatest of all in the group whose marriages have been terminated by death, divorce, or separation. The importance of this latter factor has again been substantiated by reference to the examined and diagnosed population in our study, as reported in an earlier paper.[3] Here it was shown that the per cent with rheumatoid arthritis went from 0.9 for single people, to 2.2 for married persons, and 3.6 for those in a marriage-terminated status. These rates were for men and women combined, the differences in rate among the three categories for men being even more striking.

Turning next to the interrelationship between education and income, we found among the examined and diagnosed population the same reversal of rates in the low and high education groups as that shown in Fig. 1. The differences were not as extreme but were in the same direction.

We suggest that the data on education and income make sense in terms of the hypothesis of social mobility, which postulates that those who are moving upward or downward in the social class structure are under more stress than those whose position in the structure is stable. It seems likely that low education and relatively high income may represent those who are upwardly mobile in the class structure, while high education and relatively low income may represent those who are maintaining their position precariously or moving downward in the class scale. It is thus possible that our data show an association between stress resulting from conflicts in the social structure and risk of rheumatoid arthritis. Further research on rheumatoid arthritis might well take this variable into consideration.

The association between the number of children and the prevalence of a positive index is intriguing, especially in the case of women. The finding that women with four or more children have a much higher risk for rheumatoid arthritis is well substantiated in the smaller sample of subjects who were examined

VOL.
7
1958

and diagnosed. In contemporary American society, with its emphasis on the importance of all kinds of activities outside the home, the pressures of a large family could be quite frustrating and stressful. It is interesting to carry this one step further and consider the additional variable of being reared in a large family. We have pointed out that our data here are tentative, because of small numbers, but women who come from large families and also have large families, show very high prevalence rates. The crucial factor may be pressure of work and lack of leisure time in a society which puts high value on "extracurricular" activities. We offer this only as a speculation, but feel that again further research in this area is indicated.

No ready explanation comes to mind for the association between one or two children and high prevalence rates for the men. Wondering if this might be a result of the disease, we compared the time of onset of symptoms relative to date of marriage with the number of children, as shown in Table IV. It will be noted that of the men whose onset was prior to or during the first 5 years of marriage, none had more than two children. All but two of these men had been married at least 8 or 10 years at the time of interview. On the other hand, all of the men who had more than two children reported an onset after they had been married at least 5 years. These findings may be related to a lessening in sexual interest after onset, or some interference with the procreative function, but our data were not such that we could confirm or deny this idea. Again, it may be a point worthy of consideration in further research.

TABLE IV. TIME OF ONSET OF ARTHRITIC SYMPTOMS IN RELATION TO MARRIAGE AND NUMBER OF CHILDREN FOR MALES WITH A POSITIVE INDEX OF RHEUMATOID ARTHRITIS

ONSET	NUMBER OF CHILDREN		
	0–2	3+	TOTAL
Before marriage or up to 5 years after marriage	8	0	8
6+ years after marriage	12	10	22
Total	20	10	30

In data like the ones reported in this paper, one must face the question of whether any of the factors noted are etiologically relevant or a result of the disease process. In only rare cases would low education be a result of rheumatoid arthritis. Low income, excess worries, and even termination of marriage could be resultants of the disease. A detailed study of our records indicates that this is not the case, but it is difficult to demonstrate this numerically. No spare time for leisure activities in the third decade of life is again unlikely as a result of the disease process, as is having four or more children.

Keeping in mind the problem of etiologic relevance, as well as the complexity of variables in the disease, it is worth while to point out that all we have demonstrated are certain associations between an Index of Rheumatoid Arthritis and the occurrence of certain social factors. The fact that these associations occur

seems to be clear. We have offered the interpretation that these social factors are stresses which can lead to strain within the organism, in this case rheumatoid arthritis. Many more facts must be gathered before the interpretation can be proved.

SUMMARY

1. A sample of 1,323 persons was interviewed about history of arthritic symptoms and the occurrence of certain social factors. Respondents were classified as having a positive or negative Index of Rheumatoid Arthritis and the two groups were then compared on the social data.

2. Low income, low education, and termination of marriage were associated with higher prevalence of the index for men. In the case of women the most striking factors were low education, having four or more children, reporting no spare time in the third decade of life, and worrying more than other people. The cumulative effect of grouping these factors in each sex was especially striking.

3. In particular, education and income were interrelated, with high prevalence rates noted for respondents with low education and high income, and for respondents with high education but low income.

4. The items found to be associated with a positive index were discussed in terms of the extent to which they could be considered stressful in our society, and suggestions for further research have been made.

OL.
7
958

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THE EFFECT OF INTRAMUSCULAR INJECTION OF TRYPSIN AND CHYMOTRYPSIN ON ULCERATIVE LESIONS

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VOL.
7
1958

FAVORABLE reports on the treatment of ulcerative lesions by parenteral administration of trypsin stimulated us to evaluate its use in patients with a variety of ulcerative lesions, both acute and chronic. Previous reports[1-6] dealing with the use of parenteral trypsin have not been detailed, and authors have been unable to exclude the effect of other variables such as simultaneous employment of other drugs, pressure dressings, change of environment, or use of bed rest. In the present study we have tried to exclude these variables and have observed many of our patients for a prolonged period of time; this was possible because our patients were hospitalized for long-term illness, chiefly at Longview State Hospital, a large hospital for the mentally ill.

METHODS

All patients were hospitalized before the start of therapy for variable periods up to 35 years; 27 were mental patients at Longview State Hospital, 3 were hospitalized in chronic disease hospitals, and 3 were in general hospitals. The only basis for the selection of patients was the presence of an ulcerative lesion of the skin. Of the 33 patients studied, 19 patients had ulcerative lesions of the lower extremities: 11 cases were classified as stasis ulcers, 4 were classified as arteriosclerotic lesions, 1 was on an infectious basis, 1 due to pressure, and 2 patients had long-standing ulcerations of unknown etiology. Thirteen patients had decubitus ulcers, and 1 patient had an acute ulcer with slough secondary to norepinephrine therapy for shock. In 26 of the 33 patients, lesions had not responded to previous forms of therapy including antibiotics, bed rest, soaks, various local applications, and general nutritive and supportive measures. In 7 patients of our group trypsin was initiated without previous trial of other therapy because of either the severity of the lesion or its recent discovery. In most instances the only change from the previous regime was the addition of parenteral trypsin therapy. Ambulatory patients were maintained at the same level of activity without pressure dressings.

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Most of the injections were of 3 types of trypsin: crystalline trypsin in an aqueous medium, Parenzyme (suspension of trypsin in sesame oil), and chymotrypsin, also in an aqueous medium. A few patients were given short courses of treatment with crystalline trypsin dissolved in plasma or chymotrypsin in 5 per cent gelatin; no patient received either of these throughout his entire course. The usual single dose was 2.5 mg. of the enzyme. The frequency of injections was varied and is outlined in the table. Periods of treatment and observation ranged from weeks to 2 years, and follow-up examinations were carried out on both cured and unchanged patients throughout the study. Kodachrome photographs or measurement of lesions were made at weekly intervals.

Determinations of plasma fibrinolytic activity were made on 4 of our patients at 5- and 30-minute intervals after the injection of trypsin. Two subjects had been receiving trypsin in the course of the study. Two patients were given single injections of trypsin at the time of the test. Fibrinogen levels were compared: first, by recalcification, removing the clot, and measuring the fibrinogen by the biuret technique; and second, by recalcifying, allowing the clot to remain in contact with the plasma for an hour at 37° C., and then measuring the fibrinogen in the clot.

RESULTS AND CASE HISTORIES

Of 33 patients treated, 21, or 64 per cent, showed improvement or healing; in 5, or 15 per cent, improvement was equivocal; and 7 patients or 21 per cent, showed no improvement. Of the 19 patients with lower extremity lesions, 12, or 63 per cent, showed improvement or healing; results in 3, or 16 per cent, were equivocal; and 4, or 21 per cent, showed no improvement. Of the 13 patients with decubitus ulcers, 8, or 62 per cent, showed improvement or healing; in 2, or 15 per cent, results were equivocal; and 3, or 23 per cent, showed no improvement. The patient with norepinephrine slough showed marked improvement. Local reactions to the injections, even during long-term therapy, did not necessitate interruption of therapy except in 1 patient who developed an inflammatory reaction in the right buttock at the site of injection, which subsided spontaneously (Case 8). Patients rarely complained of pain at the injection site. Fibrous nodules at the site of injection were fairly frequent, particularly after the oily suspension. No conclusions could be drawn as to the relative therapeutic value of the various preparations of trypsin or chymotrypsin employed in this study.

No evidence of plasma fibrinolytic activity was found in the tests made after single and multiple injections of trypsin, although healing of ulcerative lesions occurred in the patients who were tested. In 10 patients who died during or shortly after this study, 3 autopsies were done. Of the 10 deaths, 7 occurred during treatment with trypsin. No autopsies were performed in this group. In 2 patients, however, death may have been related to therapy. In 1 patient (Case 23) a severe generalized dermatitis, apparently due to trypsin, probably contributed to death from bronchopneumonia and cachexia. In the other (Case 32), hemorrhage from a huge decubitus ulcer led to death in a hemiplegic, debilitated patient. Similar fatal hemorrhages have been noted in this institution in patients with large decubitus ulcers treated in routine manner without trypsin.

TABLE I

NO.	PATIENT	AGE	SEX	RACE	SYSTEMIC DIAGNOSIS	TYPE ULCER	DURATION (WEEKS)	PREVIOUS TREATMENT	DOSE AND DURATION OF DRUG TREATMENT (weeks)	CONCOMITANT TREATMENT	RESULT	COMMENTS
1	R.A.	79	F	W	G.A.S.; senility	Leg—ischemic	2	Gentian violet, antibiotics, local trypsin	C 2.5 mg. t.i.d. x 4 P 2.5 mg. t.i.d. x 3		Unimproved	Died; no autopsy
2	A.M.	73	M	W	Diabetes; G.A.S.	Leg—ischemic	4	Papaverine, nicotinic acid, Priscoline, antibiotics, vitamin B_{12}	A 2.5 mg. t.i.d. x 4		Unimproved	
3	R.R.	78	F	W	G.A.S.; senility	Leg—ischemic	8	H_2O_2 irrigation	A 2.5 mg. t.i.d. x 4	H_2O_2 irrigation	Unimproved	Died
4	C.S.	77	M	W	G.A.S.; C_2H_5OH psychosis	Leg—ischemic	100	Dakin's solution; penicillin	P 2.5 mg. t.i.d. x 5 P1 2.5 mg. t.i.d. x 11 P 2.5 mg. b.i.d. x 8 C 2.5 mg. t.i.d. x 2 P 2.5 mg. b.i.d. x 1 C 2.5 mg. t.i.d. x 8	Dakin's solution	Improved	
5	G.O'B.	73	M	W	Schizophrenia; G.A.S.	Leg—undetermined	1,000	See case report in text	C 2.5 mg. t.i.d. x 13 P 2.5 mg. t.i.d. x 6		Cured	
6	R.H.	30	M	W	Undiagnosed psychosis	Leg—undetermined	?	Various local applications	P 2.5 mg. t.i.d. x 6		Cured	
7	M.B.	60	F	W	G.A.S.; senility	Foot-infectious gangrene	2	PCN, TMC ointment	P 2.5 mg. t.i.d. x 6	PCN	Cured	No improvement prior to enzyme therapy
8	A.McW.	47	M	W	Burns	Leg pressure necrosis—cast	1	None	P 2.5 mg. t.i.d. x 1		Improved	Local reaction (see case report in text)
9	J.A.	90	M	N	C.N.S. syphilis	Leg—multiple stasis	?	Various local applications	P 2.5 mg. t.i.d. x ½ P 2.5 mg. daily x 4 P 2.5 mg. t.i.d. x 6	Bed rest, PCN for few days	Cured	
10	P.C.	52	M	W	C.N.S. syphilis	Leg—multiple stasis	?	Various local applications	P 2.5 mg. t.i.d. x 20	Bed rest, pressure	Equivocal	

VOL 7 1958

OL.
7
958

11	P.DiS.	61	M	W	C.N.S. syphilis	Leg—stasis	?	None	P 2.5 mg. t.i.d. x 2		Cured	Died 6 months later
12	W.G.	50	M	W	C.N.S. syphilis	Leg—stasis	?	Scarlet red	P 2.5 mg. t.i.d. x 12		Cured	Died 1 year later; syphilitic heart disease
13	C.H.	59	M	W	C_2H_5OH psychosis	Leg—stasis	32		P 2.5 mg. t.i.d. x 9 A 2.5 mg. t.i.d. x 3 C 2.5 mg. t.i.d. x 8	Pressure Elevation Skin graft	Equivocal	
14	C.M.	70	F	W	Hysteria; G.A.S.	Leg—stasis	?	Bed rest	P 2.5 mg. t.i.d. x ½ P 2.5 mg. q.d. x 33	Bed rest Dakin's solution	Cured	
15	I.P.	68	F	W	G.A.S.; senility	Leg—stasis	?	Rest, elevation	P 2.5 mg. t.i.d. x ½ P 2.5 mg. q.d. x 19	Bed rest Cast over lesion	Cured	Role of trypsin uncertain
16	E.Q.	52	M	W	C.N.S. syphilis	Leg—stasis	?	None	A 2.5 mg. t.i.d. x 4		Cured	
17	L.S.	67	M	W	ASHD	Leg—stasis	100	None	P 2.5 mg. t.i.d. x ½ P 2.5 mg. daily x 12 P 2.5 mg. t.i.d. x 4	Pressure Bed rest	Unimproved	Trypsin alone no help; died 1 year later
18	W.W.	55	M	W	Schizophrenia	Leg—multiple stasis	?	None	P 2.5 mg. t.i.d. x ½ P 2.5 mg. q.d. x 4½ P 2.5 mg. t.i.d. x 16 C 2.5 mg. q.i.d. x 1	Pressure Elevation Polymixin	Equivocal	Trypsin ineffective without relief of stasis
19	W.W.I.	63	M	W	Mental deficiency	Leg—stasis	10	Skin graft—bed rest	P 2.5 mg. t.i.d. x 4 C 2.5 mg. t.i.d. x 2 P 2.5 mg. t.i.d. x 2 C 2.5 mg. t.i.d. x 16	Ag NO_3	Improved	
20	K.A.	78	F	W	Diabetes; G.A.S.; Parkinsonism	Decubitus	2	Caligesic	P 2.5 mg. t.i.d. x 5	Caligesic	Unimproved	Died; no autopsy
21	B.B.	57	F	W	HCVD; G.A.S.	Decubitus	±6	Soaks	A 2.5 mg. t.i.d. x 15 C 2.5 mg. t.i.d. x 3 A 2.5 mg. t.i.d. x 10	Soaks, vitamins	Improved	
22	N.C.	71	F	W	G.A.S.; senility	Decubitus	±3	Soaks	C 5 mg. b.i.d. x 5 A 2.5 mg. t.i.d. x 21	Soaks	Improved	
23	M.D.	62	F	W	C_2H_5OH psychosis	Decubitus	4	Soaks	A 2.5 mg. t.i.d. x 1 C 10 mg. q.i.d. x 1/3 A 2.5 mg. t.i.d. x 1	Soaks	Unimproved	Died; dermatitis medicamentosa

Table I continued on p. 480. For key to abbreviations, see footnotes at end of table.

TABLE I (CONT'D)

NO.	PATIENT	AGE	SEX	RACE	SYSTEMIC DIAGNOSIS	TYPE ULCER	DURATION (WEEKS)	PREVIOUS TREATMENT	DOSE AND DURATION OF DRUG TREATMENT	CONCOMITANT TREATMENT	RESULT	COMMENTS
24	A.F.	86	F	W	G.A.S.	Decubitus	±10	Soaks	A 2.5 mg. t.i.d. x 1½	Gantrisin, soaks Azochloramid	Improved	
25	H.E.	85	F	W	G.A.S.	Decubitus	16	Soaks	A.P.C. 2.5 mg. t.i.d. alternating	Azochloramid, local heat	Unimproved	Died; no autopsy
26	M.J.	70	F	W	G.A.S.	Decubitus	?	Soaks	A 2.5 mg. q.i.d. x 9	Chloresium, soaks	Cured	
27	E.J.	70	F	N	Undiagnosed psychosis	Decubitus	?	Soaks	A 2.5 mg. t.i.d. x 11	None	Cured	
28	J.K.	53	F	W	Manic depressive psychosis	Decubitus	?	Bacitracin local, Terramycin	C 5 mg. b.i.d. x 2 C 2.5 mg. t.i.d. x 2		Cured	
29	L.McL.	76	F	N	G.A.S.; senility	Decubitus	?	Azochloramid, Gantrisin	A 2.5 mg. q.i.d. x 1	Azochloramid, Gantrisin	Equivocal	Died after 1 week
30	A.S.	65	F	W	Hypertension; diabetes; hemiplegia	Decubitus	2	Furacin	A 2.5 mg. q.i.d. x 16½ P 2.5 mg. daily x 50	Furacin	Improved	
31	J.H.W.	60	M	W	C.N.S. syphilis	Decubitus	?	PCN bed rest	C 2.5 mg. q.i.d. x 10 A 2.5 mg. t.i.d. x 4 C 2.5 mg. q.i.d. x 16 A 2.5 mg. t.i.d. x 10 C 2.5 mg. q.i.d. x 8 A 2.5 mg. t.i.d. x 4	PCN	Improved	
32	L.W.	63	F	W	G.A.S.; senility	Decubitus	6	Azochloramid, Chloresium Gantrisin	A 2.5 mg. q.i.d. x 1	Azochloramid	Equivocal	Died from hemorrhage
33	G.M.	55	M	W	C.N.S. syphilis; Rheumatic heart diseases	Norepinephrine slough	2	PCN	C 2.5 mg. q.i.d. x 1½ C 2.5 mg. t.i.d. x 3	PCN	Improved	Skin graft

G.A.S. = Generalized arteriosclerosis
C = Chymotrypsin.
A = Trypsin in saline.
Pl = Crystalline trypsin in plasma.
P = Parenzyme.
CG = Chymotrypsin in gelatine.
PCN = Penicillin.
TMC = Terramycin.

VOL.
7
1958

Fig. 1.

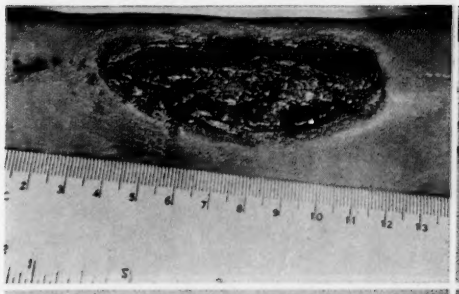
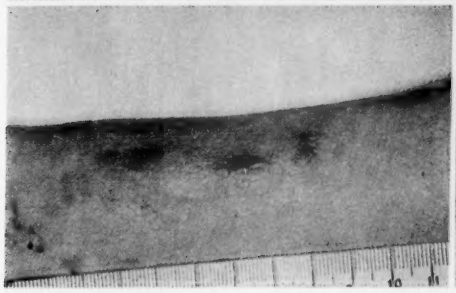


Fig. 2.

Fig. 3.



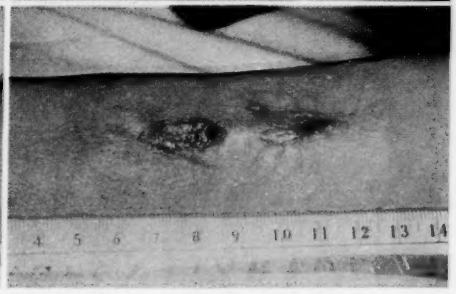


Fig. 4.

Fig. 5.

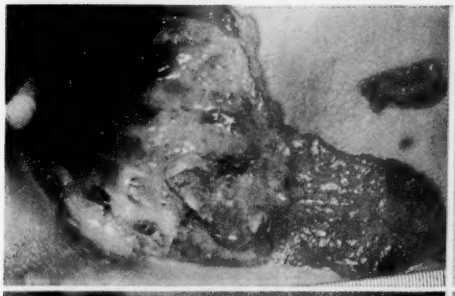


Fig. 6.

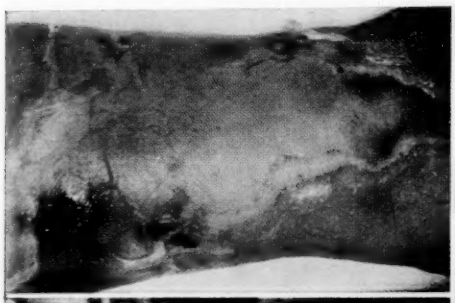
Fig. 7.

Fig. 8.

Figs. 1-4.—Case 5, C. O'B, left tibia.
Fig. 1.—May 19, 1955, before treatment.
Fig. 2.—June 18, 1955.
Fig. 3.—Aug. 18, 1955.
Fig. 4.—Sept. 10, 1955, recurrent lesion 4 weeks after cessation of therapy. Healed after 6 weeks further therapy.

Figs. 5-8.—Case 31, J. H. W. Lesion over sacrum.
Fig. 5.—May 18, 1955, before treatment.
Fig. 6.—May 29, 1955, ten days treatment.
Fig. 7.—Aug. 18, 1955.
Fig. 8.—Nov. 12, 1955.

Fig. 9.



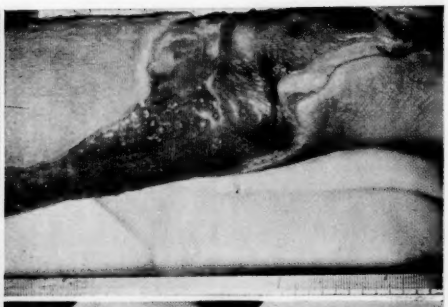
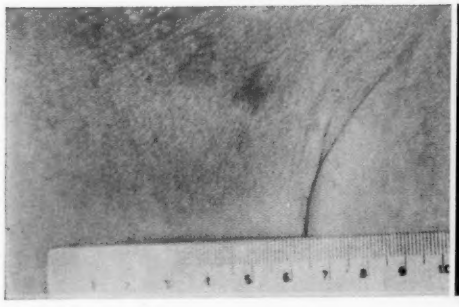


Fig. 10.

Fig. 11.

Fig. 12.

Fig. 13.



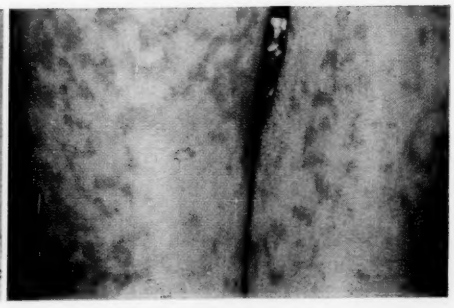


Fig. 14.

Figs. 9-12.—Case 33, G. M.
Fig. 9.—Ventral view of original lesion, May 18, 1955.
Fig. 10.—May 28, 1955.
Fig. 11.—June 11, 1955.
Fig. 12.—July 2, 1955, after skin grafting.

Figs. 13-14.—Case 23, M.D., 1955.
Fig. 13.—Anterior chest, showing dermatitis, June 11.
Fig. 14.—Legs, showing recurrence of dermatitis, June 25.

VOL
7
195

The following case reports of several interesting or unusual cases in this series are presented with Kodachrome pictures of initial lesions and various stages of healing.

CASE 5.—A 73-year-old white man had been admitted to Longview Hospital in 1911, at the age of 29, with diagnosis of dementia praecox. An ulcer on the anterior surface of the left tibia was noted in 1938, and had been diagnosed variously as gumma, carcinoma, tuberculosis, mycotic ulcer, stasis ulcer, and arteriosclerotic ulcer. Treatment had included cod liver oil locally, potassium iodide and bismuth, elevation of leg with wet dressings, skin grafting, but, apparently, the lesion had remained open. On May 19, 1955, the ulcer measured 7.5 x 3 cm., was 0.75 cm. deep, and had a sharp hard edge (Fig. 1). The tissues of the leg were atrophic and the skin was smooth. Pulses were absent in the left foot. Chymotrypsin in aqueous solution, 2.5 mg., was given 3 times daily intramuscularly. After 1 month the patient was ambulatory, the lesion was clean, shallow, and reduced in size to 4.5 x 2.0 cm. (Fig. 2). After 3 months the lesion was completely healed, and treatment was stopped (Fig. 3). On Sept. 10, 1955, 2 small recurrent lesions were noted (Fig. 4). After 6 weeks' therapy with Parenzyme, 2.5 mg., intramuscularly 3 times daily, these lesions healed and have remained healed.

CASE 31.—A 50-year-old white man with dementia paralytica and urinary and fecal incontinence was seen on May 18, 1955, with a very large, irregularly shaped ulcer over the sacrum (7.5 x 13 cm.) of unknown duration (Fig. 5). Chymotrypsin in saline 2.5 mg. 4 times daily intramuscularly was initiated. After 10 days of treatment, the lesion was granulating in remarkable fashion, with some epithelial ingrowth at the edges (Fig. 6). The lesion showed continued improvement, crystalline trypsin being substituted at times for chymotrypsin without noticeable difference in effect (Fig. 7). In 6 months the lesion had healed completely (Fig. 8).

CASE 33.—A 55-year-old white man with central nervous system syphilis and aortic insufficiency was given norepinephrine by continuous intravenous drip on May 6, 1955, for shock secondary to paroxysmal atrial fibrillation. Following accidental extravasation into the subcutaneous tissues of the forearm, an extensive area of necrosis developed. On May 18, the lesion, covered by a crust, involved almost the entire circumference of the arm, sparing 2 cm. on the radial side; it measured 12 cm. in length on the dorsal surface and 10 cm. on the anterior surface (Fig. 9). On May 18, chymotrypsin 2.5 mg. intramuscularly four times daily was begun. In 10 days the slough had separated, showing healthy granulation tissue beneath (Fig. 10). On June 11, the lesion was somewhat smaller with clean granulation tissue (Fig. 11). At this time the treatment was changed to crystalline trypsin 2.5 mg. twice daily intramuscularly in aqueous solution and continued until June 17. On June 15, 1956, skin grafting was carried out with good results. Fig. 12 shows the appearance 2 weeks after surgery.

CASE 8.—This 47-year-old white man developed a pressure ulcer 3 x 5 cm. on the left calf, 1 week after application of a cross-leg cast to immobilize his legs following a skin graft. After trypsin in oil 2.5 mg. 3 times daily had been given intragluteally for 8 days, pain, local heat, redness, and swelling were noted in the right gluteal area. No local findings were noted in the opposite buttock, although injections had been given from the same lot. Signs of inflammation disappeared in 5 days without specific therapy. The pressure ulcer practically closed. Animal tests with the vial from which the injections had been given revealed no contamination and no unusual local reaction.

CASE 23.—A 61-year-old white woman was seen on May 29, 1955, with a 1 cm. deep 4.5 x 4.0 cm. decubitus ulcer over the sacral area, which had failed to heal under therapy with Azochloramid pack, Gantrisin 1 Gm. orally 3 times daily, and multivitamins. She had previously been admitted on several occasions to the hospital ward for anorexia and marked debility. On June 1, crystalline trypsin 2.5 mg. 3 times daily intramuscularly was started. After 1 week, a generalized maculopapular eruption developed (Fig. 13), trypsin was stopped, and antihistamine therapy was given. The eruption cleared, and crystalline trypsin administration was resumed on June 18. On June 23, edema of the hands occurred, followed by a recurrence of the generalized eruption (Fig. 14). Trypsin administration was again stopped, but despite therapy with Benadryl and other measures, the skin lesions remained severe, and the patient became weaker. She died on July 12 Post-mortem examination was refused.

OL.
7
958

DISCUSSION

The mode of action of trypsin given by injection is difficult to explain since no one, including the authors, has been able to demonstrate increased plasma proteolytic activity with doses ordinarily used. However, many investigators have advanced various theories or concepts as to the mechanism of the anti-inflammatory effect and the thrombolytic effect of trypsin.

Moser[7] based on the work of Menkin,[8] Guest and associates,[9] Shulman,[10] Spector,[11] and Grob[12] believed that under the excessive local action of proteolytic substances released from organisms, leukocytes, and injured tissues, a concentration of polypeptides that stimulates the inflammatory process is produced; the natural anti-inflammatory responses of the body involve prominently an elevation of antiproteolytic activity, such activity probably residing in several different agents. Trypsin given intramuscularly, by elevation of the level of serum antiproteolytic activity, as demonstrated by Grob,[12] indirectly promotes inhibition of polypeptide production, thereby halting the local inflammatory process.

Martin[13] believes that in the initial inflammatory reaction the pore size of the protein mesh in the capillary cells and tissues is modified to permit passage into the tissue spaces of small molecular units and macromolecules. Fibrinogen passing through the protein network is converted into a labile form of fibrin thus blocking and trapping intercellular fluid. Biological continuity is eliminated, isolating the lesion. Parenteral trypsin is thought to act by transfer to the inflammatory site, causing depolymerization of the fibrin. With this depolymerization the molecular size of the fibrin is reduced and the macromolecules are removed from the protein network. Porosity is increased, intercellular fluid is released, restoring biological continuity. This permits edema and inflammation to subside and the multiple defensive forces of the blood to come into play.

Innerfield[14] advanced a similar explanation. He postulated that parenteral administration of trypsin restores the "required rate of proteolytic enzyme-protein substrate interaction at the inflammatory site, thus promoting enzymatic sequences that augment the host reaction to injury." The consequences include enhancement of phagocytosis, decreased viscosity of tissue fluids and lysis of interstitial lymphatic and capillary barriers. "Tissue permeability" and blood flow are thereby restored, and resolution of inflammation occurs in the formerly "isolated" area.

CONCLUSIONS

1. Thirty-three patients with ulcerative lesions were treated by intramuscular injections of trypsin and chymotrypsin in solution and a suspension of trypsin in sesame oil. Of this group 64 per cent showed improvement.

2. Sixty-one per cent of the 13 patients with decubitus ulcers and 63 per cent of the 19 patients with ulcerative lesions of the lower extremity showed improvement.

3. In 1 patient with necrosis following extravasation of norepinephrine solution, injection of trypsin apparently hastened separation of the slough and granulation of the wound.

4. Severe generalized maculopapular dermatitis occurred in one patient, and in another a localized inflammatory reaction developed at the site of injection and then subsided spontaneously.

5. No fibrinolytic activity was found in the plasma after single or multiple injections of trypsin.

6. The various theories for the mechanism of action of trypsin in healing are briefly summarized.

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DRUG THERAPY IN PRIMARY HYPERTENSION IN RELATION TO THE SEVERITY OF THE DISEASE

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IN AN ambulatory clinic devoted to the treatment of hypertension, the response to therapy with a variety of drugs was evaluated in 116 patients over a period of 3½ years. The mean period of observation of patients under treatment was 9.3 months ± S. D. of 7.6 months.

Blood pressures were measured in the erect and supine positions many times before and during treatment in all patients. Also, the usual historical and clinical studies were carried out in each case to exclude patients with hypertension secondary to such diseases as chronic glomerulonephritis, chronic pyelonephritis, polycystic kidneys, pheochromocytoma, Cushing's syndrome, and coarctation of the aorta. The drugs used for treatment were Rauwolfia serpentina derivatives, including crude root, alseroxylon fraction, reserpine, rescinnamine, and recanescine; Veratrum derivatives, including various Veratrum extracts and protoveratrine; phenoxybenzamine hydrochloride, hydralazine hydrochloride; and both orally and parenterally administered ganglion blocking drugs, including hexamethonium and pentolinium. These drugs were administered singly to some patients and in different combinations to others.

The patients were divided into three groups according to the severity of the disease. The "mild" group consisted of those patients with persistently elevated blood pressure but no evidence of organic involvement. The "severe" group consisted of those patients with more elevated blood pressure, and involvement of two or more organs, such as kidney, heart, or brain, and with Grade 2 to 4 retinopathy. The "moderate" group were patients somwehere between the mild and severe.

Response to treatment was also divided into three groups, "good," "fair," and "poor." A good response was considered to be a substantial drop in blood pressure to normal or near normal levels together with regression, where present, of other objective manifestations of the disease, as in the kidneys, eyegrounds, or

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VOL
7
195

heart. A poor response was no change or an equivocal change in blood pressure with no regression of the other manifestations of the disease, whereas a fair response was somewhere between the good and poor response.

RESULTS

The results are summarized in Tables I, II, and III. The blood pressures recorded prior to treatment are the lowest and highest of from three to ten readings regardless of the position of the patient when the blood pressure was determined. The blood pressures during treatment are the lowest maintained pressures and represent an average of at least 3 blood pressures in each case. Where wide discrepancies occurred, the lowest and highest blood pressures were recorded.

A good response was observed in 42 per cent of the 116 patients treated, 58 per cent exhibiting a fair to poor response. The effect of treatment was better in the initial or mild stage of the disease (good response in 20 of the 30 cases) than in the moderate (good response in 9 of the 20 cases) or severe stage (good response in 20 of the 66 cases). The other manifestations of hypertension, including subjective symptoms, heart size, eyeground changes, electrocardiographic evidence of heart strain, also reverted toward normal in many of the patients in whom the blood pressure was significantly lowered.

Our experiences with the various drugs used did not differ significantly from those reported by others.[1-28] The various rauwolfia preparations were all similar in their effects provided equivalent dosages were employed. The usual side actions of diarrhea, nasal stuffiness, drowsiness, etc., were encountered without necessitating cessation of therapy. The most serious side action of the rauwolfia drugs was psychic depression. This always made cessation of therapy mandatory but was not encountered in this series in more than 5 per cent of the cases.

The Veratrum drugs were used sparingly and with diminishing frequency as time went on. They seemed to add but little to therapy with rauwolfia drugs. Tolerance developed frequently, and anorexia, nausea, and vomiting often became problems as the dosage was increased. Phenoxybenzamine hydrochloride was used only once and achieved a temporary reduction in blood pressure in that case.

Hydralazine hydrochloride seemed to have its chief value in the more advanced cases of hypertension. A dosage of 300 mg. daily was never exceeded, and no case of lupus erythematosus-like reaction was encountered. The other annoying side actions, such as angina pectoris, tachycardia, skin eruption, dyspnea, edema, diarrhea, nausea, and vomiting, were not uncommon and occasionally necessitated cessation of therapy.

The ganglion blocking drugs, like the rauwolfia drugs, had actions similar to each other. Pentolinium seemed more readily absorbed from the intestinal tract than hexamethonium, and on parenteral administration the effect of pentolinium seemed more prolonged than that of hexamethonium. Hexamethonium and pentolinium were administered either parenterally or orally in 17 cases. Experiences with mecamylamine and chlorisondamine are not recorded in this series. The most important side action was collapse, brought on at least in part,

TABLE I. MILD HYPERTENSION

PATIENT	CASE NO.	AGE AND SEX	DURATION OF HYPER-TENSION	BLOOD PRESSURE BEFORE TREATMENT		DRUGS USED	DURATION OF TREATMENT	BLOOD PRESSURE AFTER TREATMENT	REMARKS
				MINIMUM	MAXIMUM				
W.D.	2	46 M	5 yr.	212/104	230/110	Rauwolfia	1 yr.	130/82	Good response
L.F.	8	68 F	?	190/106	200/106	Rauwolfia	6 mo.	130/80	Good response
C.G.	13	60 F	2 yr.	150/92	180/96	Veratrum	2 mo.	190/100	Poor response
R.G.	14	53 F	8 yr.	184/102	200/104	Hydralazine	2½ yr.	138/80	Good response
M.S.	28	38 M	7 yr.	130/80	154/110	Rauwolfia	9 mo.	114/84	Good response, very small dosage required
S.S.	36	80 F	?	188/99	255/110	Rauwolfia	3 mo.	200/90	Poor response
R.S.	37	70 F	5 yr.	170/90	250/130	Rauwolfia	4 mo.	190/110	Poor response
F.T.	38	50 F	5 yr.	160/90	160/92	Rauwolfia	4 mo.	130/80	Good response, myxedema
J.S.	39	34 F	2 yr.	160/100	200/130	Rauwolfia	5 mo.	180/100	Poor response
						Rauwolfia and hydralazine	5 mo.	182/102	Poor response
I.T.	40	47 F	5 yr.	160/120	195/110	Placebo	1 mo.	144/94	Placebo treatment only
E.M.	58	43 F	6 yr.	205/110	300/160	Rauwolfia	4 mo.	180/110	Fair response
P.P.	64	53 F	3 yr.	140/80	190/100	Rauwolfia	14 mo.	140/80	Good response
G.P.	71	36 F	8 yr.	170/110	220/150	Rauwolfia	1 yr.	150/96	Good response
M.D.	88	50 M	8 yr.	190/106	194/110	Rauwolfia	5 mo.	162/90	Good response
S.R.	96	50 F	1 yr.	174/110	210/120	Rauwolfia	1½ yr.	162/98	Good response
M.F.	106	75 F	3 yr.	220/104	280/140	Rauwolfia	4 mo.	162/92	Good response
S.S.	108	73 F	20 yr.	175/85	200/110	Rauwolfia	16 mo.	168/82	Good response
						Hydralazine, not tolerated			
P.A.	122	47 M	5 yr.	180/110	190/120	Rauwolfia	6 mo.	178/88	Good response
M.A.	123	4 F	7 yr.	160/110	160/116	Rauwolfia	2 mo.	124/72	Good response
E.A.	125	55 F	7 yr.	184/110	200/120	Rauwolfia	2 mo.	164/100	Fair response
S.B.	126	72 F	25 yr.	150/90	168/110	Rauwolfia and hydralazine	3 mo.	160/80	Fair response
H.B.	129	50 F	1 yr.	170/100	200/110	Rauwolfia	18 mo.	148/88	Good response
C.B.	138	63 F	16 yr.	200/100	220/110	Hydralazine	3 yr.	150/80–172/80	Good response, some escape later
R.A.	143	47 M	2 yr.	180/110	200/120	Rauwolfia	6 mo.	140/84	Good response, acromegaly
E.J.	153	40 F	1 yr.	156/102	220/130	Rauwolfia	5 mo.	180/116	Poor response
H.J.	159	64 F	17 yr.	170/100	190/110	Rauwolfia	3 mo.	130/80	Good response
P.H.	172	27 F	1 yr.	155/108	194/120	Rauwolfia	1 yr.	148/100	Poor response
R.K.	174	56 F	18 yr.	166/89	174/110	Rauwolfia	6 mo.	176/82	Poor response
H.H.	180	50 F	18 yr.	210/120	180/110	Rauwolfia and hydralazine	8 mo.	140/90–182/104	Initial good response; then escaped

VOL. 7 1958

VOL. 7 1958

TABLE II. MODERATE HYPERTENSION

PATIENT	CASE NO.	AGE AND SEX	DURATION OF HYPER-TENSION	BLOOD PRESSURE BEFORE TREATMENT		DRUGS USED	DURATION OF TREATMENT	BLOOD PRESSURE AFTER TREATMENT	REMARKS
				MINIMUM	MAXIMUM				
R.E.	5	60 F	5 yr.	156/104	194/120	Rauwolfia	6 wk.	190/108	Poor response
D.F.	7	68 F	22 yr.	240/120		Rauwolfia	5 mo.	220/124	Poor response
D.P.	10	48 F	20 yr.	190/90	182/118	Rauwolfia	3 wk.	190/104	Poor response
						Hydralazine	4 mo.	152/98	Fair response
M.S.	29	73 F	15 yr.	170/100	200/110	Rauwolfia	7 mo.	140/88	Good response
M.T.	34	50 F	?	206/112	210/120	Rauwolfia	5 mo.	170/110	Fair response
F.S.	43	56 F	8 yr.	196/100	210/130	Veratrum	3 mo.	170/110	Poor response
						Rauwolfia	5 mo.	184/100	Fair response—poor
R.Mc.	46	40 F	5 yr.	220/100	260/130	Pentolinium (P.H.) and rauwolfia	18 mo.	140/92	Good response to pentolinium but marked side actions
M.M.	51	45 F	7 yr.	140/110	220/140	Rauwolfia	6 mo.	190/110	Poor response
						Pentolinium (P.O.)	3 mo.	140/100	Good response
V.M.	52	70 M	24 yr.	190/90	242/130	Rauwolfia and pentolinium (P.O.)	6 mo.	190/100	Poor response
								174/110	Would not continue pentolinium (toxicity)
L.M.	62	39 F	?	170/100	190/110	Rauwolfia and Veratrum	3½ yr.	170/110	Fair response
A.Z.	73	71 F	5 yr.	204/112	240/120	Rauwolfia	7 mo.	168/80	Good response
M.R.	99	54 M	20 yr.	150/100	200/110	Rauwolfia	6 mo.	148/82	Good response
D.R.	117	57 M	34 yr.	190/110	274/170	Rauwolfia and pentolinium (P.H.)	3 mo. in hospital	208/120	Poor response Psychiatric features
G.W.	118	56 F	?	160/95	250/140	Hydralazine	2 mo.		Hydralazine stopped quickly; toxicity; good response to rauwolfia
						Rauwolfia	3 yr., 6 mo.	160/76	
M.C.	140	57 F	7 yr.	200/104	220/120	Rauwolfia	1 yr.	140/100	Good response
S.C.	141	56 F	5 yr.	230/158	260/150	Rauwolfia	3 mo.	230/118	Poor response
L.R.	149	65 F	2 yr.	174/104	190/120	Rauwolfia and hydralazine	2 yr.	160/80	Good early response Escaped later
J.H.	155	48 F	3 yr.	150/92	150/100	Rauwolfia	3 mo.	130/84	Good response
E.L.	161	48 F	2 yr.	170/120	210/140	Rauwolfia	9 mo.	135/80	Good response
E.K.	166	72 F	5 yr.	170/100	200/120	Rauwolfia	10 mo.	180/104	Poor response, diabetes
G.L.	169	56 M	12 yr.	210/110	220/110	Rauwolfia	1 yr.	196/112	Poor response
						Rauwolfia, hydralazine, and Veratrum	7 mo.	190/106	Poor response

TABLE III. SEVERE HYPERTENSION

PATIENT	CASE NO.	AGE AND SEX	DURATION OF HYPER-TENSION	BLOOD PRESSURE BEFORE TREATMENT		DRUGS USED	DURATION OF TREATMENT	BLOOD PRESSURE AFTER TREATMENT	REMARKS
				MINIMUM	MAXIMUM				
D.J.	1	61 F	10 yr.	250/100	285/100	Rauwolfia	3 mo.	280/110	Poor response
J.D.	3	51 M	2 mo.	218/154	256/154	Hexamethonium (P.H.)	5 mo.	220/150	
						Veratrum	4 mo.	210/150	
						Rauwolfia	20 mo.	130/90	Good response to rauwolfia only
L.E.	4	52 F	2 yr.	210/140	230/136	Rauwolfia	6 wk.	210/140	
						Hydralazine	2 mo.	215/135	
						Combined	3 mo.	170/110	Fair response to combined treatment
A.F.	9	33 F	1½ yr.	220/132	230/130	Hydralazine	3 mo.	192/132	Poor response
I.L.	44	68 M	10 yr.	204/120	220/150	Rauwolfia	8 mo.	230/130	Poor response
V.G.	11	34 F	12 yr.	220/130	260/140	Pentolinium (P.O.) and rauwolfia	4 mo.	240/142	Poor response; previous sympathectomy without benefit; also rice diet
R.G.	12	60 F	15 yr.	220/108	240/112	Rauwolfia	2 mo.	220/110	
						Rauwolfia and hydralazine	4 mo.	230/110	Poor response
T.G.	15	63 F	10 yr.	186/100	188/102	Rauwolfia	4 wk.	165/90	Fair response
J.G.	16	60 M	12 yr.	240/140	260/130	Hydralazine	4 mo.	208/114	Poor response
						Rauwolfia	9 mo.	174/100	Fair response
R.G.	17	69 F	10 yr.	200/110	210/110	Rauwolfia	3 mo.	190/110	Poor response
J.G.	18	56 F	6 yr.	200/120	240/140	Rauwolfia	4 mo.	210/120	Poor response
B.H.	20	58 F	6 yr.	184/110	238/116	Hydralazine and rauwolfia	6 mo.	164/90–212/100	Temporary lowering, followed by escape
N.H.	21	53 M	1 yr.	200/118	244/140	Hydralazine and rauwolfia	1 yr.	210/110	Poor response
S.H.	22	55 F	5 yr.	160/100	184/100	Rauwolfia	4 mo.	180/100	Poor response
G.H.	23	37 F	10 yr.	180/110	200/110	Hydralazine	3 mo.	190/110	
						Rauwolfia	4 mo.	195/110	Poor response
I.H.	24	64 M	15 yr.	190/90	210/110	Rauwolfia	2 mo.	230/110	Poor response
M.H.	25	52 M	7 yr.	220/120	250/140	Hexamethonium	1 wk.	230/130	
						Hydralazine and rauwolfia	1 yr.	140/74	Good response to combined treatment
E.S.	26	27 F	13 yr.	184/150	220/160	Rauwolfia	2 mo.	210/140	Poor response
						Rauwolfia and hydralazine	1 yr.	158/122	Fair response
T.S.	27	51 F	?	220/110	230/140	Hydralazine	4 mo.	210/120	
						Rauwolfia, hydralazine, and Veratrum	6 mo.	180/86	Fair response to combined treatment
H.S.	30	30 M	?	175/138	200/130	Hydralazine	3 mo.	142/104	Fair response
B.S.	31	50 F	14 yr.	208/108	244/128	Rauwolfia	5 mo.	200/110	Poor response

VOL. 7 1958

H.S.	32	22	M	?	216/160	250/140	Hexamethonium (P.O.) and hydralazine	6 mo.	204/150	Poor response
							Rauwolfia	2 yr.	156/104	Fair response
G.S.	33	62	F	10 yr.	170/80	210/110	Rauwolfia	18 mo.	160/84	Good response
U.T.	35	64	F	12 yr.	220/110	240/120	Rauwolfia	1 yr.	210/130	Poor response
J.L.	45	77	M	10 yr.	190/100	238/110	Rauwolfia	3 mo.	120/70	Good response
A.M.	47	60	M	9 yr.	210/110	240/140	All drugs available	1 yr.	220/130	Died; malignant nephrosclerosis with cerebral hemorrhage, uremia
C.M.	48	48	M	3 yr.	190/100	230/130	Hydralazine	1 mo.	185/95	
							Rauwolfia	1 mo.	190/105	Fair response (period of observation short)
S.M.	49	41	F	2 yr.	188/94	240/140	Rauwolfia	3 yr., 6 mo.	160/94, 146/92	Good response
D.M.	53	67	M	10 yr.	180/90	240/110	Rauwolfia	6 mo.	224/119	Poor response
B.M.	56	60	F	20 yr.	150/90	250/130	Rauwolfia	6 mo.	160/95	Poor response
B.M.	60	54	M	9 yr.	190/120	224/130	Rauwolfia	3 mo.	200/130	
							Hydralazine	3 mo.	210/130	Poor response
							Veratrum	1 mo.	200/120	
							Pentolinium (P.O.) and rauwolfia	4 mo.	194/108	Fair response to pentolinium and rauwolfia
L.M.	61	68	M	?	210/120	300/150	Rauwolfia	18 mo.	180/90	Congestive heart failure; fair response to rauwolfia
A.V.	68	40	M	1½ yr.	180/100	250/140	Veratrum	4 mo.	250/140	Poor response
							Hydralazine	3 mo.		
T.P.	70	63	F	23 yr.	190/96	280/170	Rauwolfia	1 yr.	240/140	Poor response
							Dibenzyline	1½ mo.		
M.Y.	80	46	F	9 yr.	196/116	300/160	Rauwolfia	18 mo.	156/90	Good response
J.OF.	81	54	M	3 yr.	206/92	210/130	Rauwolfia and Veratrum	2 yr.	160/90–175/95	Fair response; congestive heart failure developed under treatment
J.P.	82	49	F	14 yr.	250/142	262/150	Pentolinium (P.O.)	3 mo.	220/130	Poor response; prior sympathectomy
D.D.	89	61	F	8 yr.	190/96	250/100	Rauwolfia and hydralazine	1 mo.	164/66	Fair response
S.S.	94	45	F	7 yr.	172/140	220/160	Hexamethonium (P.H.)			Hexamethonium not tolerated
							Hydralazine	9 mo.	148/80	Good response to hydralazine
J.R.	98	45	M	10 yr.	216/124	250/152	Rauwolfia	4 mo.	180/110	Fair response
C.R.	115	62	F	7 yr.	204/114	230/130	Rauwolfia and hydralazine	1 yr.	140/100	Good response
I.B.	127	41	F	15 yr.	215/134	232/128	Hydralazine and hexamethonium (P.H.)	4 mo.	158/98	Temporary response only
							Pentolinium (P.O.) and rauwolfia	2 yr.	170/102	Temporary response only; in congestive heart failure
C.A.	128	44	F	1 yr.	212/120	250/134	Rauwolfia	9 mo.	170/100	
							Hydralazine	6 mo.	140/90	Good response to hydralazine
A.B.	130	70	F	7 yr.	190/90	210/112	Rauwolfia	18 mo.	190/90, 140/84	Fair response
M.B.	132	67	F	10 yr.	190/120	234/118	Rauwolfia	6 mo.	138/72	Good response
J.B.	133	56	M	3 yr.	190/120	214/118	Rauwolfia and hydralazine	7 mo.	178/98	Fair response
R.C.	134	32	F	13 yr.	210/140	220/160	Rauwolfia	1 yr.	152/96, 160/106	Good response
M.C.	135	78	M	3 yr.	165/95	190/90	Rauwolfia	4 mo.	176/76	Fair response

TABLE III. SEVERE HYPERTENSION (CONT'D)

PATIENT	CASE NO.	AGE AND SEX	DURATION OF HYPER-TENSION	BLOOD PRESSURE BEFORE TREATMENT		DRUGS USED	DURATION OF TREATMENT	BLOOD PRESSURE AFTER TREATMENT	REMARKS
				MINIMUM	MAXIMUM				
A.D.	136	35 F	9 yr.	170/94	200/120	Rauwolfia	4 mo.	192/104	Poor response
G.A.	137	42 F	11 yr.	204/142	300/160	Rauwolfia	3 yr.	188/106	Fair response
						Veratrum	1 mo.	220/116	
S.B.	139	53 F	1 yr.	275/152	275/160	Pentolinium (P.O.)	2 mo.	160/80–190/80	Early good response; later escaped
W.B.	142	37 F	2 yr.	168/110	190/120	Rauwolfia	3 mo.	120/80–130/90	Good response
C.B.	144	44 F	10 yr.	210/136	190/135	Rauwolfia and pentolinium	5 mo.	146/104–196/120	Fair response to pentolinium and rauwolfia
						Hydralazine	3 mo.	196/125	
S.R.	145	61 F	18 yr.	240/116	250/110	Hydergine	3 mo.	164/84–200/100	Poor response
						Rauwolfia	6 mo.		
C.R.	146	54 F	8 yr.	245/150	220/130	Rauwolfia	1 yr.	136/100–150/110	Fair response
F.R.	147	68 F	10 yr.	160/120	222/140	Rauwolfia	4 mo.	170/100–210/100	Poor response
L.K.	150	63 F	3 yr.	232/120	250/130	Rauwolfia and hydralazine	8 mo.	204/100	Tuberculosis; poor response
M.K.	152	67 F	8 yr.	194/94	220/130	Rauwolfia and hydralazine	1 yr.	210/110	Poor response
V.I.	154	65 F	14 yr.	190/94	210/120	Rauwolfia	4 mo.	210/110	Poor response
						Veratrum	5 mo.	220/94	Poor response
L.H.	160	48 F	4 yr.	160/100	190/120	Rauwolfia	5 mo.	180/100	Poor response; treated in hospital
J.K.	164	64 F	17 yr.	180/106	200/120	Rauwolfia	6 mo.	180/100–150/80	Poor response
H.H.	165	56 F	2 yr.	170/110	230/120	Rauwolfia and hydralazine	8 mo.	130/100–132/90	Fair response
J.M.	170	56 F	6 yr.	190/94	210/120	Rauwolfia	14 mo.	170/82	Good response
L.K.	171	55 F	20 yr.	210/110	230/120	Rauwolfia	2 yr.	220/115	
						Hydralazine	6 mo.	178/90	Good response to hydralazine alone
						Veratrum	6 mo.	210/110	
L.K.	175	61 F	20 yr.	230/110	240/140	Rauwolfia	5 mo.	230/120	Poor response; thyroid disease treated
A.K.	176	54 F	3 yr.	200/100	230/90	Rauwolfia	3 mo.	154/70–130/90	Good response

VOL. 7 1958

by postural hypotension. The most annoying side action was constipation. This could be combated with some success by pilocarpine and neostigmin cathartics, and enemas. Collapse was avoided by regulation of dosage and occurred less frequently with parenteral than with oral medication and less frequently with the better absorbed drug. Blurring of vision, dry mouth, impotence, and bladder dysfunction were also observed occasionally. Impotence could be corrected by strategic omission of a dose of the drug. Tolerance to all these preparations developed within a period of several weeks and dosage had to be increased accordingly to maintain the desired effect.

DISCUSSION

These experiences indicate that drug therapy is effective in lowering the blood pressure and in modifying the course of primary hypertension in at least 42 per cent of ambulatory patients treated, the remaining 58 per cent being relatively unaffected by therapy with the usual drugs. There is hope that this 58 per cent of relative unresponsiveness may be reduced further by the more vigorous use of drugs such as hydralazine and by salt depletion, both of which seem to affect the intrinsic blood flow or resistance rather than the neurogenic factor,[22,29] and also by the use of more potent drugs directed at the neurogenic factor where that can be demonstrated to exist. The more favorable effect of treatment in the "mild" than in the "severe" group, in this series as well as in others,[30] would seem to favor earlier treatment.

SUMMARY AND CONCLUSIONS

One hundred sixteen patients with primary hypertension were observed under treatment with drugs administered singly or in various combinations over periods varying from 1 month to 3½ years. The drugs used were Rauwolfia serpentina derivatives, including crude root, alseroxylon fraction, reserpine, rescinnamine and recanescine; Veratrum derivatives, including various Veratrum extracts and protoveratrine; phenoxybenzamine hydrochloride; hydralazine hydrochloride; and both orally and parenterally administered ganglion blocking drugs, including hexamethonium and pentolinium salts. The response to therapy was better in the early mild than in the more advanced severe hypertensive patient.

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VOL. 7 195

DIGITAL CIRCULATORY TESTING IN PRIMARY HYPERTENSION WITH REFERENCE TO SEVERITY OF THE DISEASE AND TO DRUG THERAPY

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IT HAS been shown in previous studies that neurogenic vasoconstriction is increased in the digits of patients with primary hypertension in comparison with normotensive subjects.[1] It has also been demonstrated that in these hypertensive patients there is a decrease in the intrinsic caliber of digital blood vessels over that of normotensive subjects, as determined from flow-pressure ratios (radius equivalents) in the vasodilated state.[1,2] An attempt was hence made to correlate these values as obtained from digital circulatory tests, both with the severity of the disease and the subsequent results of therapy. These tests were performed in 41 patients selected at random from 116 patients treated. In 8 of these 41 patients, the tests were repeated during the period of treatment with drugs, and in 5 patients during a period of treatment with placebos.

The circulatory test was carried out as follows: blood pressure and blood flow were measured in the third or fourth digit by methods already described,[1,3] both at rest in bed at room temperature varying between 26 and 29° C. and also after inhibition of sympathetic nerve discharge by indirect heat for one-half an hour or more until sweating appeared, supplemented by the intravenous injection of 0.8 mg. per kilogram of 2,6 dimethyl-1, l-diethyl piperidinium bromide (SC 1950). By methods described elsewhere[1] the flow-pressure ratios were converted into radius equivalents of the dilated and constricted blood vessels and the work and force of vasoconstriction were calculated.

Several precautions must be exercised in the interpretation of these tests. Room temperature during the test must be maintained between the indicated limits. If this is not done, the results become more difficult to interpret. If

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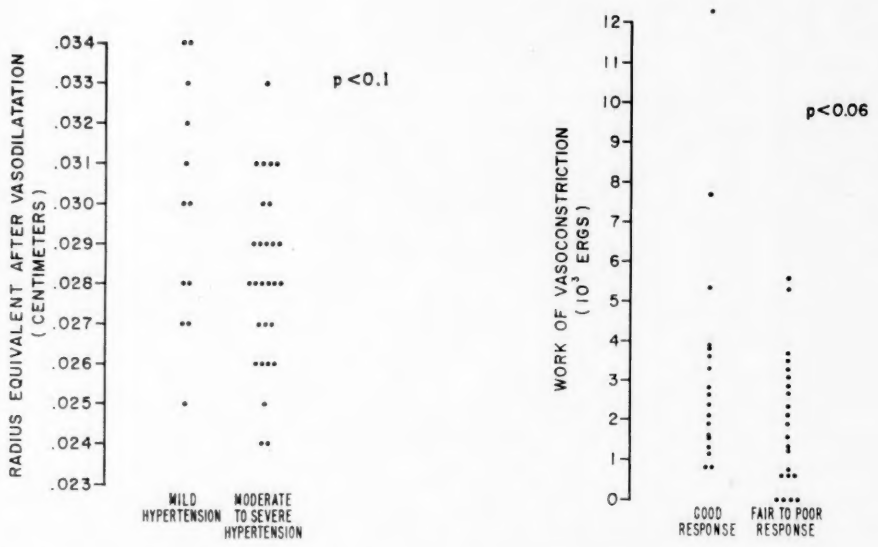

Fig. 1.—Relationship between clinical classification of primary hypertension and digital vascular caliber after vasodilatation.

Fig. 2.—Relationship between work of vasoconstriction determined prior to therapy and response to treatment.

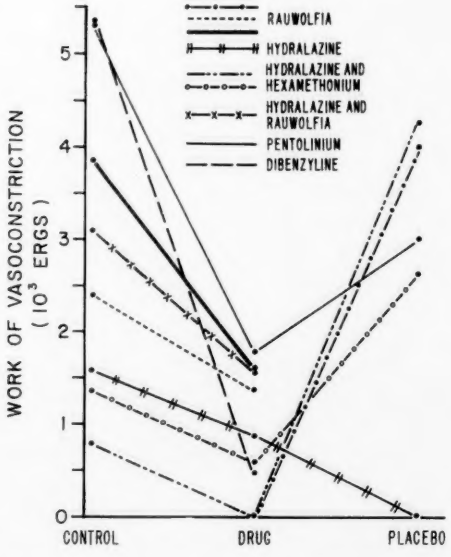

Fig. 3.—Effect of drugs on digital vasoconstriction

blood flow after vasodilatation in a patient not in the malignant phase of hypertension is well below the lower limit of normal, the test should be repeated. This will happen in from 5 to 10 per cent of patients tested. If patients with complicating overt peripheral vascular disease, such as Raynaud's disease or thromboangiitis obliterans, are tested, the results will require special interpretation. Patients with severe complications of hypertension, such as cerebrovascular accidents, coronary occlusion, heart failure or uremia, should be tested, if at all, with great caution. We have had no single untoward effect from the test in this series and in a much larger series of normotensive patients, despite the fact that the test is done by a technician under the supervision of a physician, who gives the injection. A device for elevating the foot of the bed in case unusual hypotension is produced, should be available, as should norepinephrine and methoxamine hydrochloride. We have never, in this series, had to employ any measure other than elevation of the foot of the bed, and that in only an occasional patient.

VOL.
7
1958

The disease in each patient was classified as "mild," "moderate," or "severe" on the basis of clinical criteria already set forth, and the response to therapy as "good," "fair," or" poor" according to standards previously described.[4,5] No significant differences were found between the "moderate" and "severe" groups or between those with a "fair" or "poor" response with reference to digital circulatory studies. The "moderate" and "severe" groups were therefore consolidated and compared with the "mild" group; and also the groups with a "fair" or "poor" response were consolidated and compared with the group having a "good" response.

RESULTS

There was no correlation between the severity of the disease and the extent of the increase in neurogenic vasospasticity as measured by the work of vasoconstriction. The only value that could be correlated at all with the clinical estimate of severity was the intrinsic digital vascular caliber or radius equivalent (derived from the flow-pressure ratio) in the vasodilated state. The difference between the "mild" and the "moderate to severe" groups, however, was significant only to the $p < 0.1$ limit of confidence, so that only values at the lower or upper extremes were of any diagnostic or prognostic value in an individual patient (Fig. 1, Tables I and II).

Response to therapy could be correlated only with digital vasoconstriction of sympathetic nervous origin as measured by the work of vasoconstriction prior to treatment. This correlation, too, was imperfect, the difference between the "good" and the "fair to poor" responders, as far as digital vascular work was concerned being significant only to the $p < 0.1$ level. Only in those cases at either extreme, that is, with very high or especially with very low or no vasoconstrictive work values, could digital circulatory studies to be used to predict the response to therapy (Fig. 2, Tables I and II).

It is clear, however, from Fig. 3 and Table II that in the 8 cases studied the work of vasoconstriction could always be demonstrated to decrease when the patient was under treatment with a variety of drugs and to increase again with placebo therapy in 4 of the 5 cases studied. The fifth case in which it decreased with placebo was probably one of those familiar instances in which a patient with

TABLE I. RESULTS OF DIGITAL CIRCULATORY TESTS PRIOR TO TREATMENT

CASE NO.	SEVERITY	BEFORE VASODILATATION				AFTER VASODILATATION				WORK OF VASOCONSTRICTION 10^3 ERGS	RESPONSE TO TREATMENT
		BRACHIAL BLOOD PRESSURE MM. Hg	DIGITAL BLOOD PRESSURE MM. Hg	DIGITAL BLOOD FLOW $CM.^3/CM.^2$ SKIN/MIN.	RADIUS EQUIVALENT CM.	BRACHIAL BLOOD PRESSURE MM. Hg	DIGITAL BLOOD PRESSURE MM. Hg	DIGITAL BLOOD FLOW $CM.^3/CM.^2$ SKIN/MIN.	RADIUS EQUIVALENT CM.		
128	Severe	220/120	204/112	0.15	0.021	170/102	165/114	0.24	0.024	2.67	Good
8	Mild	180/100	132/54	0.17	0.029	102/58	76/36	0.29	0.034	1.91	Good
172	Mild	190/124	164/106	0.15	0.024	140/90	132/84	0.20	0.025	0.62	Poor
165	Severe	180/130	102/52	0.02	0.022	120/82	98/60	0.23	0.029	3.70	Fair
171	Severe	210/108	178/72	0.12	0.024	120/70	106/60	0.26	0.029	2.84	Good
149	Moderate	180/104	144/80	0.23	0.027	90/60	80/40	0.20	0.030	1.18	Fair
43	Moderate	210/118	160/100	0.20	0.025	132/90	144/100	0.31	0.028	1.59	Poor
30	Severe	150/100	132/70	0.21	0.027	126/88	120/80	0.29	0.028	0.63	Fair
39	Mild	188/110	158/79	0.27	0.029	152/90	122/64	0.36	0.031	1.21	Poor
137	Severe	204/140	190/130	0.18	0.024	108/90	120/80	0.24	0.027	1.93	Fair
132	Severe	192/116	180/90	0.27	0.027	140/74	130/72	0.31	0.029	1.28	Good
89	Severe	208/88	180/70	0.31	0.028	100/54	142/80	0.29	0.028	0.00	Fair
138	Mild	210/80	144/70	0.10	0.024	110/60	100/66	0.21	0.027	1.62	Good
16	Severe	230/120	195/106	0.31	0.027	150/90	134/94	0.34	0.028	0.73	Poor
17	Severe	200/110	170/96	0.15	0.024	130/80	104/60	0.23	0.028	2.10	Poor
20	Severe	190/108	192/80	0.08	0.023	160/92	136/62	0.30	0.029	3.32	Good
23	Severe	212/110	160/100	0.18	0.026	135/90	115/75	0.39	0.031	3.30	Poor
53	Severe	170/110	158/130	0.16	0.025	118/90	104/80	0.44	0.033	5.61	Poor
152	Severe	205/120	180/90	0.21	0.027	135/70	114/48	0.30	0.031	2.13	Poor
88	Mild	194/110	185/115	0.28	0.027	150/85	160/100	0.36	0.028	0.79	Good
161	Moderate	150/110	134/92	0.10	0.022	140/96	115/80	0.28	0.026	3.61	Good
81	Severe	180/126	190/85	0.22	0.025	130/85	125/85	0.22	0.026	0.59	Fair
46	Moderate	230/100	180/83	0.03	0.012	164/104	152/96	0.29	0.027	12.27	Good
82	Severe	260/140	204/104	0.16	0.023	236/140	170/100	0.25	0.027	2.87	Poor
145	Severe	220/100	140/90	0.10	0.023	120/60	80/40	0.23	0.031	3.51	Poor
40	Mild	162/124	160/80	0.12	0.025	140/100	110/50	0.32	0.032	3.82	Poor
34	Moderate	202/100	160/86	0.16	0.026	126/78	114/54	0.31	0.031	2.71	Fair
31	Severe	244/124	187/90	0.24	0.025	150/94	158/76	0.21	0.025	0.00	Poor
68	Severe	244/144	220/88	0.19	0.024	218/140	200/86	0.23	0.024	0.00	Poor
118	Moderate	166/110	110/80	0.12	0.024	130/90	105/75	0.21	0.026	1.18	Good
32	Severe	150/100	128/88	0.19	0.026	140/110	128/88	0.20	0.026	0.00	Poor
162	Mild	200/120	160/80	0.02	0.019	120/90	120/70	0.34	0.030	7.72	Fair

VOL 7 1958

TABLE II. RESULTS OF DIGITAL CIRCULATORY TESTS PRIOR TO AND DURING DRUG TREATMENT AND DURING PLACEBO TREATMENT

CASE NO.	SEVERITY	DRUGS	BEFORE VASODILATATION			WORK OF VASOCONSTRICTION 10^3 ERGS	BRACHIAL BLOOD PRESSURE MM. Hg	AFTER VASODILATATION			BRACHIAL BLOOD PRESSURE MM. Hg	RESPONSE TO TREATMENT
			DIGITAL BLOOD PRESSURE MM. Hg	DIGITAL BLOOD FLOW CM.^{3}/CM.^{2} SKIN/MIN.	RADIUS EQUIVALENT CM.			DIGITAL BLOOD PRESSURE MM. Hg	DIGITAL BLOOD FLOW CM.^{3}/CM.^{2} SKIN/MIN.	RADIUS EQUIVALENT CM.		
124	Mild	Rauwolfia	97/54	0.10	0.024	0.00	124/60	114/50	0.11	0.024	158/96	Fair
		Placebo	151/106	0.13	0.021	3.97	140/80	126/71	0.23	0.027	180/106	
140	Moderate	Rauwolfia	153/102	0.10	0.023	2.35	170/100	150/97	0.26	0.026	180/100	Good (eventually)
		Hydralazine	180/130	0.35	0.028	1.65	102/72	90/65	0.32	0.031	200/110	
14	Mild	Control	150/80	0.33	0.030	1.56	130/74	150/50	0.43	0.033	160/80	Good
		Hydralazine	105/45	0.36	0.034	0.84	110/60	95/40	0.39	0.036	120/58	
		Placebo	120/50	0.23	0.028	0.00	120/70	100/50	0.21	0.028	145/75	
180	Mild	Control	170/145	0.06	0.020	5.34	130/90	105/80	0.26	0.027	192/110	Fair
		Pentolinium	124/84	0.08	0.023	1.79	130/80	120/74	0.20	0.026	140/92	
		Placebo	166/104	0.17	0.025	3.00	104/76	126/80	0.31	0.029	176/108	
26	Severe	Control	180/140	0.23	0.026	3.09	130/110	124/94	0.39	0.030	194/150	Poor
		Hydralazine and rauwolfia	164/124	0.12	0.022	1.59	162/130	148/120	0.25	0.025	176/130	
29	Moderate	Control	124/70	0.22	0.029	2.39	104/62	84/50	0.36	0.034	196/94	Good (eventually)
		Rauwolfia	133/50	0.23	0.032	1.36	144/76	94/45	0.37	0.035	170/85	
108	Mild	Control	160/100	0.11	0.024	3.84	130/80	110/70	0.33	0.030	200/110	Good (eventually)
		Rauwolfia	132/92	0.15	0.025	1.58	146/82	108/56	0.22	0.028	180/100	
127	Severe	Control	170/110	0.27	0.027	0.77	155/100	155/100	0.35	0.028	184/110	Poor
		Hydralazine and hexamethonium	115/70	0.33	0.030	0.00	130/90	110/56	0.30	0.030	150/100	
		Placebo	170/120	0.15	0.024	4.25	130/80	156/94	0.40	0.029	180/106	
2	Mild	Control	180/104	0.06	0.020	5.37	140/95	138/88	0.29	0.027	180/100	Good
		Dibenzyline	124/102	0.22	0.027	0.47	96/72	88/62	0.22	0.028	156/98	
134	Severe	Control	186/100	0.26	0.027	1.35	164/126	160/70	0.33	0.029	210/142	Good (eventually)
		Hexamethonium and hydralazine	180/80	0.29	0.028	0.59	170/130	168/65	0.32	0.029	196/142	
		Placebo	200/140	0.19	0.024	2.66	170/120	164/104	0.34	0.027	200/140	

neurogenic hypertension responds to any kind of attention or treatment. The only other effect observed in these studies was an increase in intrinsic digital vascular caliber in cases where hydralazine was given, although this was not consistent.

DISCUSSION

It is apparent that digital circulatory studies are in general not well correlated with the severity of primary hypertension except perhaps as the disease approaches the so-called "malignant" phase. This is not unexpected, since it is known that the arteriolosclerosis associated with hypertension involves different arterial beds in varying degree and at a varying pace.

What is more, most cases cannot be selected or rejected for treatment on the basis of digital circulatory studies alone unless they show extreme vasospasticity, on the one hand, or little or none, on the other. This may be considered an inherent limitation of the technique or perhaps even a failure to effect adequate vasodilatation by means of the testing procedure in the more severe cases. Another possible explanation of the results, however, is that the predictive value of the test was not as good as it might have been because some patients were inadequately treated. Treatment of ambulatory patients must necessarily be more conservative than that of hospitalized patients and is more often limited by side actions of drugs, patient resistance, and other factors. With improvement of therapy with saluretics it might be possible along with the effects of hydralazine to observe a more consistent increase in intrinsic digital vascular caliber.[6,7] Also the use of more potent and easily managed ganglion blocking drugs which can be given by mouth and are now available might make it possible to move some of the patients from the "fair to poor" into the "good" group of responders to treatment. This could increase the predictive value of the test in the future and thus provide a means for indicating in more cases when treatment should be pursued more vigorously and when withheld or administered with caution.

SUMMARY

1. Digital circulatory tests were carried out prior to treatment in 41 cases of primary hypertension and repeated during a period of treatment with drugs in 8 patients, and during a period of placebo therapy in 5 patients.

2. Intrinsic vascular caliber as derived from the flow-pressure ratio in the vasodilated state was somewhat decreased in the "moderate to severe" as compared to the "mild" cases.

3. Neurogenic vasoconstriction as measured by the work of digital vasoconstriction was somewhat increased prior to treatment as measured in the "good" as against the "fair to poor" responders. The overlap, however, was too great for individual predictions except for the extreme values.

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VOL 7 195

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OL.
7
958

Review

A CRITICAL REVIEW OF THE EFFICACY OF MEPROBAMATE (MILTOWN, EQUANIL) IN THE TREATMENT OF ANXIETY

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VOL. 7 1958

INTRODUCTION

THIS paper will attempt to review and evaluate the published experimental evidence on the efficacy of meprobamate (Miltown, Equanil) in the management of anxiety. We will not include those studies that discuss anxiety only indirectly. That such a review is needed is indicated by the rapid and extremely wide acceptance accorded the compound since it was introduced in 1955. Thus, according to Krantz and Carr's pharmacology textbook[1]: "There is perhaps no other drug introduced in recent years which has had such a broad spectrum of clinical application as has meprobamate. As a tranquilizer, without an autonomic component in its action, and fraught with a minimal (sic) of side effects, meprobamate has met a clinical need in anxiety states and many organic diseases with a tension component. That it has met this clinical need is evinced by the fact that it is the most frequently prescribed of all drugs today."

Beckman,[2] in his textbook, writes: "The tranquilizing, or ataraxic, properties of this drug are outstandingly exemplified in psychoneurotic individuals with the irrational fears and dreads characterizing the anxiety state, and in lessening the bodily tensions, irritability and difficulty in concentrating of such persons."

The Council on Pharmacy and Chemistry of the American Medical Association[3] states that meprobamate seems to be useful ". . . as a tranquilizing agent that can be employed in place of potent sedatives and along with psychotherapy in the management of psychoneurotic anxiety and tension states."

The published papers are reviewed in four sections, corresponding to the different kinds of patients studied: (1) psychiatric outpatients and private

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office patients; (2) hospitalized psychiatric patients; (3) patients with anxiety accompanying physical complaints and therapeutic procedures; and (4) alcoholics. There then follows a section on the comparison of meprobamate with standard drugs used for the same reasons, and, finally, our conclusions.

In discussing the papers reviewed in this article, we have been guided, as to our confidence in the results, by the degree of experimental control exercised by the investigators; that is, the degree to which possible sources of bias were removed or compensated for. The minimum precautions needed to collect data free of bias are outlined in numerous sources (e.g., Bradford Hill,[4] Finney,[5] Lasagna[6]). These include: (1) random allocation of subjects to the various treatment groups or to different sequences of treatments; (2) inclusion of a group receiving placebo or "standard medication"; and (3) ignorance, on the part of both observers and subjects, of which patients receive which treatments. Only a handful of the studies on meprobamate meet these criteria. The objection that double blind designs militate against the discovery of real effects is so nonsensical that we shall not bother to discuss it.

We have not tried to evaluate the reliability or validity of the techniques used to gauge response to the drug. But we would like to note that, for the most part, these techniques seem to be singularly inadequate, and reflect a lack of appreciation that a reliable index of effect is needed in order to make a reliable judgment of efficacy.

NEUROTIC AND PSYCHOTIC OUTPATIENTS AND PRIVATE OFFICE PATIENTS

The two studies that first reported impressive results for meprobamate in clinical psychiatry are those by Borrus[7] and by Selling[8]. These studies appeared in the same issue of the *Journal of the American Medical Association*. They are the papers most frequently referred to by subsequent writers. For these reasons we will discuss them in some detail.

Borrus studied 104 patients, 59 men and 45 women, "who were a random selection from those referred to me in private practice for neuropsychiatric examination and treatment during a 12 month period in 1953-1954." The actual procedure used in selecting patients is not given. Patients received one to six 400 mg. tablets of meprobamate daily for lengths of time varying from 2 weeks to 6 months. Dosage was not specified more precisely. Sixty-seven were diagnosed as showing anxiety reactions, either acute or chronic. The other 37 patients fell into eight categories, ranging all the way from drug addiction through schizophrenia to reactive depression, with no one of these categories including more than 9 patients. We will therefore focus our attention upon the anxiety reactions.

The 67 patients diagnosed as displaying anxiety reactions were divided into four groups at the end of the study. Twenty (30 per cent) were labelled "recovered." Included here were "patients whose symptoms subsided completely, both subjectively and objectively, and who returned to work and became socially productive." Twelve (18 per cent) fell into a "very favorable" category: "patients in whom the symptoms subsided considerably, subjectively and objectively, and who, when they returned to work, became socially productive and either tolerated the minor symptoms or were undisturbed by them." Twenty (30 per

cent) showed "some favorable effect": "patients in whom there were some favorable effects after medication, subjectively, and who became socially productive but were still looking for something further in the way of improvement." And 15 patients (22 per cent) "reported no effects on their symptoms from medication."

These results are striking. If they adequately reflected the performance of the drug it would be fair to say that a major advance in the management of anxiety had been made. Unfortunately, no such conclusion is possible. The control procedures necessary to insure valid results were not followed. No attempt was made to collect the data without bias: the physician who made the evaluations knew what the patient was taking, and no placebo controls were used. Borrus did use patients who had "failed to respond to mephenesin and barbiturate therapy." (The barbiturates are not again mentioned but the author mentions in his discussion that the anxiety reaction patients received a 2-week course on mephenesin—to which "they had either failed to respond or felt only a slight effect from it"—before they were started on meprobamate.) This procedure might help to screen out some of the patients who would react favorably to anything given them by a physician. It is not a control procedure that will insure that any effect found at the end of the experiment is in fact due to the drug given during the course of the trial. It can be especially misleading when the length of time covered is many months, given the amount of spontaneous change to be expected in neurotic patients. And it can be even more misleading when the physician apparently does not limit his participation to an impersonal doling out of tablets. Borrus states: "The effectiveness of Miltown in anxiety and tension states is very encouraging and emphasizes its value as *an adjunct to psychotherapy*." (Italics ours.) This leads us to believe that the glowing results of the clinical trial may be, at least in part, a glowing tribute to Borrus's ability as a psychotherapist. Unfortunately, given the experiment as it is reported, it is impossible for the reader to conclude anything at all about the unique contribution of the drug.

The Selling study was also performed on office patients. Selling treated 187 subjects, usually with 400 mg. t.i.d., for from less than one to more than 15 months. Of these, 43 were diagnosed as showing tension states and 29 as showing anxiety states; 19 were diagnosed as conversion hysterics, 16 as showing involutional depression. The other 80 patients were distributed over 12 other categories. Seventeen of the tension state cases (40 per cent) were "recovered," 24 (56 per cent) were "improved." Ten of the 29 anxiety state patients (34 per cent) were "recovered"; 17 (59 per cent), "improved." Comparable figures for the 19 conversion hysterics are 6 (32 per cent) "recovered," 6 (32 per cent) "improved"; for the 16 involutional depression cases, 6 (38 per cent) "recovered" and 7 (44 per cent) "improved."

These results are once more remarkable and once more uninterpretable. "All patients had regular sessions of psychotherapy in addition to treatment with the drug," says Selling. Logically, the results, even if trustworthy, are as much evidence for the efficacy of the psychotherapy as they are evidence of the potency of the drug. But in the absence of an adequate control group nothing can be concluded from the data reported. Selling did recognize the necessity for some

sort of control and switched 16 patients from the drug to placebos. He reports: "Before the end of a week, all of them complained so much about the return of their symptoms that they had to be returned to Miltown therapy immediately." This attempt to control for some of the factors that could be accounting for the purported drug effect fails for at least two reasons. First, the author does not tell his readers just how the 16 patients who were switched in this way were chosen. Of what subgroup of the 187 patients were they representative? Second, Selling was not "blind" in making his determinations of improvement or lack of improvement after the placebo therapy. It is not known to what extent bias has entered into these judgments.

The enthusiastic reports of Borrus and Selling have been followed by a barrage of other enthusiastic, uncontrolled, clinical reports. A fair proportion of these are so poorly executed or reported that they warrant no discussion. We will also disregard casual observations (Dixon[9]), case studies (Ruchwarger,[10] Follin, Sigg, Pivet, and Girard[11]), and experimental studies on fewer than 10 subjects (Dierkens and Van Reeth[12]). A few uncontrolled studies will be discussed in each section of this review. These will be chosen because they either give some surface appearance of validity, illustrate a common defect in experimental design, or have been widely cited.

Uncontrolled studies, usually reporting excellent results, were made by Osinski,[13] Schneider and Villa,[14] Jurquet-Maillet, Rance and Roger,[15] Floris and Rambelli,[16] Catalano-Nobili and Cerquetelli,[17] Genevard,[18] Berglund, Blumenthal, and Flordh,[19] Hørsdal,[20] Fasanaro and Ventra,[21] Millen,[22] Bolzani,[23] Jares, Cione, and Ragazzi,[24] Dierkens and Van Reeth,[12] West and daFonseca,[25] and Folkson.[26] With all the sources of bias that can influence uncontrolled observations, especially under these conditions, it is impossible to conclude anything at all from these reports.

McLaughlin[27] reported on a 2-year study of 34 out-patients, who, it was said, had not responded under previous psychiatric treatment. These patients were informed that they were going to receive a new drug, and that it would not cure them, but would "probably help them." Almost all (32) of the patients improved. But, in addition to meprobamate, treatment included individual and group psychotherapy, E.C.T., visits to patients' homes by a psychiatric nurse, and help from social agencies. It is rather dangerous to infer from such a study that improvement, even if demonstrated—and there is no conclusive evidence for this—is due, even in part, to the drug.

Phillips[28] also confounded drug administration and psychotherapy, as did Dickel, Dixon, Wood, and Shanklin,[29] whose patients also were taught Jacobson's technique of progressive relaxation. Gardner[30] made the same type of error. Kaufmann, Burner, and Trollux[31] did not use a placebo, they wrote, because the drug had already been shown, by others, to be effective. Moreover, their patients were encouraged to believe that they would be helped by the medication. In addition, most of the patients were undergoing psychotherapy at the time. It is hardly surprising that the authors reported beneficial results.

Besides performing the uncontrolled studies listed above, West and daFonseca[25] and Folkson[26] made controlled studies of the drug. The former

VOL.
7
1958

authors compared meprobamate (400 mg. t.i.d. plus 400 to 800 mg. at night) and placebo in a double blind study of 26 outpatients with chronic anxiety. Half of the group started on each treatment, then switched to the other after the next visit to the clinic. Patients varied in the number of times they returned to the clinic and thus in the number of judgments they made of the benefit derived from treatment. A total of 71 such judgments were analyzed. The authors report the number of judgments that were categorized "Benefit" and "No benefit" under each of the two treatments. Under meprobamate 21 of these judgments were scored "Benefit" while 14 were scored "No benefit." Under placebo the totals were 12 for "Benefit" and 24 for "No benefit." A chi-square test proved significant, but it is inappropriate because the judgments were obviously not independent, several being contributed by each subject (Lewis and Burke[32]). It is therefore impossible to evaluate the data presented. It might be noted also that the method used to report the results of the trial did not take advantage of the fact that each patient had served as his own control. The correct analysis for data of this type is given by Siegal.[33]

Folkson[26] studied 23 outpatients in a double blind fashion. Only patients "showing tension irrespective of diagnosis" were used, with "the great majority . . . suffering from either acute or chronic anxiety states, or depression associated with tension." He gave them either placebos or meprobamate 400 mg. t.i.d. or q.i.d., raising the dosage after a while to 800 mg. t.i.d. or q.i.d. in 5 cases. Patients were switched to the alternative treatment at each visit to the clinic. How much time elapsed between visits was not specified. The length of the trial averaged two months.

Only 3 of the 23 patients showed improvement on the drug and not on the placebo. The rest either showed equal improvement with both treatments or did better on placebo.

Another double blind study was carried out by Koteen.[34] He used 25 patients who presented symptoms of "anxiety, muscle tension, restlessness and irritability." The physician gave the patient a coded bottle of 50 tablets of either meprobamate or placebo, telling him "he was receiving a new drug which might be of help to him. He was told further that if the agent failed to be of help he would be given a larger dose the next time." Regardless of whether he reported being helped or not, the patient received another bottle of tablets whose contents were unknown to both patient and physician. The dosage was usually 400 mg. three or four times a day, but in some cases the dosage apparently was tripled.

A total of 73 bottles, 37 of the drug and 36 of placebo, were judged by the 25 patients. Patients varied greatly in the number of judgments that they contributed: 2 took only one bottle each before stopping participation; 3 took eight or nine bottles each. The author pools all 73 judgments to show that 21 of the 37 bottles of meprobamate and 23 of the 36 bottles of placebo effected improvement. This method of tabulating the data is the same as that used by West and daFonseca[25] and the same objections apply. However, Koteen gives 6 case histories which account for half the data in the study. It can be inferred, from inspection of these, that a more sophisticated analysis of the raw data

would not refute the author's conclusion that he could find no difference between the drug and placebo in relieving the symptoms shown by his patients.

Far and away the most sophisticated clinical trial on outpatients was done by Raymond, Lucas, Beesley, O'Connell, and Roberts.[35] They studied a heterogeneous group attending an outpatient psychiatric service. Almost all patients attending during the period of the trial were used, the criterion for inclusion being only that they had a "tension component" in their symptomatology. The following drugs, in the daily doses given, were studied: amobarbital (Amytal) 300 mg., benactyzine (Suavitil) 6 mg., chlorpromazine 150 mg., meprobamate 2,400 mg., "Sedaltine" (a preparation including 1.50 mg. Rauwolfia, 55 per cent alkaloids, 600 mg. mephenesin, 390 mg. Bromvaletone, 1,170 mg. Carbromal, and 600 mg. aluminum hydroxide), and placebo. Each patient was given the six treatments for successive 2-week periods. "He was told that he was taking part in a trial to find out which of several tablets was best for him." Each day he recorded his judgment of the effect of the drug on a five-point scale, ranging from "very poor" to "very good." Both patient and physician were kept unaware of the identity of the particular treatment in use at any given time.

VOL.
7
1958

Seventy-nine patients started the study, but only 51 yielded data. Four turned in unusable forms, and 24 stopped coming to the clinic before the whole trial ended. These dropouts were shown not to be related systematically to the particular drug the person was on when he failed to return. Thus, it is probable that they did not bias the study. The order of treatment was so balanced as to make comparisons among drugs solely the reflection of differences among drugs, with several conceivably biasing factors held constant.

The results were straightforward. The amobarbital proved significantly better than all the rest ($p = 0.05$). The other drugs and the placebo did not differ among themselves. In terms of the average response, on amobarbital 9 patients called it poor or very poor, 9 found no effect, and 33 said it was good or very good. Comparable figures for meprobamate are 17, 9, and 25; for placebo, 21, 8, and 22; for chlorpromazine, 26, 6, and 19; for benactyzine, 23, 10, and 18; and for Sedaltine, 22, 4, and 25.

HOSPITALIZED NEUROTIC AND PSYCHOTIC PATIENTS

Meprobamate has also been used to treat hospitalized mental patients. The studies reported in this section deal with this facet of its use. Most of these suffer from the same lack of experimental rigor that is typical of the studies reported in the other sections.

For instance, Collomb, Miletto, and Chaupin[36] treated 36 patients ranging in diagnostic category from chronic schizophrenia to tension states and report that 80 per cent of these responded favorably to meprobamate. Tension states, psychomotor agitation, and insomnia were apparently most affected by the drug. No controls were used, although the authors state that 23 of the 36 were previously treated with chlorpromazine, reserpine, or shock, and did not respond. The necessity for a concurrent control group seemed not to be appreciated.

Uncontrolled observations have also been offered by Smigel,[37] Bower,[38] Collomb and Miletto,[39] Favier, Juillet, Bernat, and Lapierre,[40] Ferrari,[41] Hift,

Krypsin-Exter, and Solms,[42] Hormia,[43] Kaufmann, Burner, and Trollux,[31] Müller,[44] Micheletti and Inga,[45] and Racamier, Blanchard, and Faueret.[46]

Pennington's report of her study[47] of 300 psychotics is somewhat confusing. One hundred of her patients were on placebo for 2 months before being put on meprobamate for an unspecified length of time. Two hundred were never given placebos. The results for all 300 are lumped together in one table. On page 257, the beginning dose is stated to be "two 400 mg. tablets twice a day." But on page 259, a case that began with a dose of ten 400 mg. tablets twice per day is reported. In her table, 9 of the 300 patients are listed as complete remissions, while in a paragraph on the same page it is stated that 60 patients had left or were waiting to leave following meprobamate treatment. Pennington's results are further clouded by her report that one of the patients accumulated a hoard of 62 tablets by saving those given to her plus those "*discarded by other patients.*" (Italics ours.) Was there no control, then, over dosage and dosage schedule? In view of these and other contradictions, any conclusions based on the data presented are gratuitous. The author also makes several statements about the drug's action. For instance, she says that the drug "calms and quiets without clouding consciousness." How the relative cloudiness of consciousness was measured is not stated. It is said that the patient's "environment does not disturb him. Logical thinking returns and in many cases, when environmental tensions lessen, delusions and hallucinations are obviated with the support afforded his ego by this medication." If data exist on these points, they are not presented in the published report.

Pennington[48] also reported a double blind study on 196 psychotic patients, each of whom had a one-month trial on each of five drugs plus two one-month trials on placebo. The trials were separated from one another by an unspecified number of days. No information is given about the order in which treatments were administered, nor about how evaluations of improvement were made. On the two one-month trials on placebo, 68 per cent and 42 per cent of the patients showed at least "some improvement." Comparable figures for the drugs are 59 per cent for meprobamate 1,600 mg. per day; 61 per cent for azacyclonol (Frenquel) 80 mg. per day; 69 per cent for chlorpromazine 200 mg. per day; and 62 per cent for Rauwolfia (Raudixin) 400 mg. per day; and 62 per cent for reserpine 4 mg. per day. No attempt was made to test any of these differences for statistical significance, but it seems obvious that there is none.

Laird, Angelo, and Hope[49] used chronic schizophrenic females in two small studies. Blind evaluations at several levels of complexity were made, but the small number of patients involved—each study compared 4 patients on meprobamate with 4 on placebo—makes it impossible to assess the reliability of the changes found.

Gorfinkel and Kline (reported in Barsa and Kline[50]) studied the effects of meprobamate 2,400 mg. per day on 25 chronic schizophrenic patients. The drug was given for 9 months. No control group was used. Nothing but a rapidly disappearing mild sedation was noticed. Since the method of observing patient behavior is not specified, the possibility remains that real changes effected by the drug were missed.

Barsa and Kline[50] used several drug combinations on 36 schizophrenics who had failed to respond satisfactorily to trials of unstated length of reserpine and chlorpromazine, either alone or in combination. They used four groups, giving one meprobamate alone, pairing the meprobamate with either reserpine or chlorpromazine in the next two, and giving all three drugs in the fourth. Since they did nothing to guard against observer bias, apparently did not constitute their treatment groups in a random fashion (there were 5, 6, 17, and 3 patients in the four groups), and used no placebo control group, nothing about meprobamate can be concluded from the study.

Hertz and Kronholm[51] did a double blind study with 76 hospitalized neurotics, using meprobamate 1,200 mg. per day and placebo, and switching patients from one treatment to the other every 3 weeks for four such periods. Which treatment came first for a particular patient was randomly determined. Nurses made ratings on some 17 symptoms each day. The authors conclude that the drug was useful in reducing several symptoms, including anxiety and restlessness, but their analysis is difficult to accept. Their patients completed 219 out of a possible total of 304 3-week periods. All the ratings for a given period were summarized, and the period was judged as showing either improvement or no improvement. The code was then broken. For 164 of these periods it was found that the subjects' behavior corresponded to what would be expected if the drug was active and the placebo not. In the remaining 55 periods such congruence did not exist. The authors then looked at the records for these latter periods; "it was found that the patients in this group had had especially severe psychotraumata." The data for these periods were therefore ignored in the analysis— a procedure that seems wholly unwarranted. Throwing away these data invalidates the authors' later attempt to estimate the effects of the drug on individual symptoms.

Hollister and his associates used meprobamate in two studies of hospitalized patients. One, by Hollister, Elkins, Hiler, and St. Pierre,[52] was a double blind study of 37 patients, 27 of whom were schizophrenic. Fifteen were given placebos, while the rest received 400 mg. q.i.d. meprobamate for 5 days, 800 mg. q.i.d. for the next 5 days and 1,200 mg. q.i.d. for the last 11 days of the trial. Only 2 of the 15 placebo patients were judged to have improved versus 13 of the 22 receiving the drug. It is difficult to evaluate these data since the two treatments were presented with very different challenges: all of the 15 patients receiving placebos were diagnosed as schizophrenic, while only 12 of the 22 (54 per cent) receiving the drug fell into that category.

The second study, by Hollister, Stannard, and Drake,[53] was of 24 hospitalized patients, all of whom showed anxiety as the predominant symptom. Most were labeled neurotic, but 4 were said to have a "schizophrenic reaction of the pseudoneurotic type with no disorganization of personality or distortion of reality." They received alternate 21-day courses of meprobamate 3,200 mg. per day and placebo. Agreement among ward personnel, psychiatrist, and patient was demanded if the patient was to be scored as improved. Using this stringent criterion, 11 patients were helped only by the drug, 3 only by placebo, with the remaining 10 responding similarly to both and therefore contributing no data on

the drug-placebo comparison. The authors provided no statistical test of the reliability of the obtained difference. Our analysis of these data yielded a chi-square of 3.50 (McNemar's test; see Siegal[33]). For df = 1, this is not significant at the 0.05 level (two-tailed test).

Heller, Walton, and Black[54] evaluated meprobamate on a group of 32 hospitalized neurotics who were selected for study because they showed symptoms of tension "manifested mainly by restlessness, insomnia, headaches, irritability, and panic attacks." The patients were broken into groups of 16 each by matching individuals on the basis of the Taylor Manifest Anxiety Scale, and two arbitrarily chosen groups of questions from the Minnesota Multiphasic Personality Inventory, one of which was concerned with tension, the other with headaches. One group was given meprobamate 400 mg. t.i.d.; the other was given placebos. The trial was double blind and lasted four weeks.

The number of patients showing "very marked," "marked," or "some minor" improvement, "no change," and "deterioration" were 1, 2, 5, 7, 1 fo placebo and 6, 2, 5, 3, 0 for meprobamate. This difference was not subjected to any statistical test by the authors. We coded the ratings, calling "very marked" improvement five and "deterioration" one, and performed a Mann-Whitney U test (see Siegal[33]) to ascertain whether the two groups differ on these ratings. They do, with p = 0.05 (two-tailed test), thus leading us to believe that meprobamate led to more improvement than did placebo.

The anxiety, tension, and headache scales were repeated at the conclusion of the trial and the changes from their initial administration analyzed. No significant changes were found when drug and placebo groups were compared. The data were then looked at for two separate subject subgroupings. Nineteen patients (9 on drug, 10 on placebo) were called "dysthymics" (anxiety states, reactive depressions, obsessional neuroses); 13 of the patients (6 on drug, 7 on placebo) were called "hysterics" (hysterics, sociopathic and inadequate personalities). On one scale, "tension," for one group, "dysthymics," a decrease significant at the 0.05 level was found (t = 2.26, df = 17). In view of the number of statistical comparisons made, the small number of subjects involved, and the unspecified reliability of the scale used, this finding can be taken as no more than a hint for further research.

Jensen, Kristjansen, and Paerregaard[55] investigated the effects of meprobamate in two groups of hospitalized patients. One group consisted of 19 neurotic patients showing acute symptoms of anxiety. The other consisted of 17 patients who were in a state of senile agitation and confusion. Patients were given either placebo or meprobamate for from 10 days to 2 weeks. Dosage was usually 1,600-2,400 mg. per day. The treatment a patient received was determined by lot. Clinical evaluations were made by two of the authors who were not involved in assigning treatments and who, consequently, made their judgments blind. About half of the patients were switched to the other agent at the end of the first trial. The authors report and analyze these additional data with that from the initial trials. Such a procedure is difficult to defend. We shall report the results of the initial trial alone, a procedure which, incidentally, does not change any of their conclusions.

In the neurotic group, 6 of the patients who received meprobamate showed a definite change for the better, and 3 showed no change. Comparable figures for the placebo group were 3 and 7. This split is not significant if tested by Fisher's exact probability test (Siegal[33]). All 8 of the senile patients on the drug improved while only 3 out of 9 on placebo did so. This difference is significant by the Fisher test ($p = 0.014$; two-tailed test). The authors state that the drug lessened the confusion and agitation found at night with these patients and improved their sleep.

Tucker and Wilensky[56] studied 63 schizophrenic patients who had been ill at least 18 months and who were selected because they showed overt anxiety or tension. Meprobamate was given to 32 patients, placebo to the other 31. Personnel evaluating the patients were kept blind as to which were receiving the active medication. The trial consisted of a 2-week premedication period during which base line observations by a psychiatrist and nursing personnel were made, a 12-week medication period, and a 4-week postmedication period. The starting dosage was 400 mg. q.i.d. of either placebo or drug and was increased by 400 mg. q.i.d. every two weeks until 1,200 mg. q.i.d. was reached if the particular patient was not considered improved. By the sixth week, after which further increases were not made, all but 8 patients were receiving the maximum dosage. Pills were discontinued abruptly at 12 weeks.

At the end of the 12 weeks on medication, the psychiatrist judged 72 per cent of the 32 patients on the drug and 42 per cent of the 31 patients on placebo as showing less observable anxiety than during the premedication period ($p = 0.02$). This change disappeared 4 weeks after medication ceased. The psychiatrist's ratings showed no differences on subjective reports of either psychologic or physical symptoms.

The nursing personnel also noted a significant difference for anxiety and tension at the 12-week point (66 per cent improved on drug versus 29 per cent on placebo). This difference remained significant on the postmedication rating. A personality inventory of anxiety items that was given just before, near the end, and 2 weeks after the medication period failed to reveal any statistically reliable changes, although only 60 per cent of the patients yielded analyzable data.

Global ratings, made on the basis of all available data, showed "significant improvement" in 13 of the 32 drug patients (41 per cent) and 3 of 31 placebo patients (10 per cent). This difference is reliable ($p = 0.01$). Significant improvement means ". . . improvement of such a magnitude that patients previously exhibiting many of the signs of anxiety and tension manifested clear reduction or disappearance of such phenomena." Only 3 drug patients and one placebo patient continued at this level of improvement 4 weeks after withdrawal of the drug.

TREATMENT OF ANXIETY ACCOMPANYING PHYSICAL COMPLAINTS, DIAGNOSTIC OR THERAPEUTIC PROCEDURES

Many workers have attempted to study the effects of meprobamate on anxiety accompanying various physical complaints or induced by a preceding or forthcoming therapeutic or diagnostic procedure.

Kessler and Barnard[57] studied various types of cancer patients who were in pain while on home care. They reported "good" results in 23 out of 51 patients. LeVan[58] reported that 80 per cent of a group of 224 patients suffering from various dermatoses gave a favorable response to the drug. Viglioglia and Linares,[59] and Kaminsky, Sevinsky, and Kaplan[60] also found it useful for anxiety accompanying dermatologic disorders. Garat, Berruezo, Orciveli, Cullen, and de Novoa[61] studied 15 patients with allergies, first giving 1,200 mg. meprobamate a day for 10 days, then placebo for a like period. They reported improvement with drug, even on the Rorschach, in several patients, Michelet[62] found it useful in asthmatics. Balduini[63] and Altschul and Billow[64] claimed it useful in the management of several medical conditions where a functional component was suspected. The latter found that, in a group of 93 such patients, 23 per cent were rendered symptom-free, and an additional 42 per cent had some diminution of symptoms. Steinberg and Roodenburg[65] gave it to 26 patients of psychogenic rheumatism. Of these, 22 showed a satisfactory clinical response. Brage[66] found the drug helpful in many neurologic cases. Leimgardt and Kittel[67] reported good results with ulcer patients, women with pre- and postclimacteric symptoms, and various autonomic complaints, as did Laberke,[68] who gave the drug to patients with assorted physical complaints. Ermiglia[69] reported excellent success in treating dysmenorrhea and in ameliorating climacteric symptoms. Belafsky, Breslow, and Shangold[70] say it is useful in pregnancy. Ricciardi and Rugiero,[71] and Garavaglia[72] say it made women more comfortable during labor. Cicala[73] found it useful in allaying anxiety associated with intestinal symptoms from appendicitis and typhoid fever. Lund and Anholm[74] used it to control the anxieties of dental patients about to undergo surgical or prosthetic treatment.

All of the studies just listed suffer from fatal defects in design or execution. In none of these was an adequate control group run along with the drug group.

Dunsmore, Dunsmore, Bickford, and Goldman[75] claimed that meprobamate provided "symptomatic relief of varying degrees in 19 of 21 hypertensive patients." Pentolinium therapy was also given. Since no control group receiving pentolinium therapy alone was run it is difficult to see how one can be sure that changes are due to the meprobamate.

Some authors, like Friedman,[76] recommend meprobamate for chronic headache. In the study reported by Friedman, it is stated that about half the study was conducted in double blind fashion, but the design of the study and the method for assigning patients are not given. Of 210 patients used, 150 complained of tension headaches and 60 of migraine headache. Improvement was noted in 55 per cent of the migraine and 67 per cent of the tension headache patients. The author states, "The results must be compared with our present placebo response of approximately 58 per cent improvement in migraine and 46 per cent in tension headache, and with previous reports of favorable placebo response in 50 per cent in migraine and 58 per cent in tension headache." Does this mean, as implied, that the placebo observations are based on data collected on other groups and at other times? If so, the comparisons are meaningless, and vitiate the whole concept of control. Further, what proportion of the improvements are contributed by the double blind study? More confusion is added by Fried-

man's casual remark that amphetamine was administered to patients taking large amounts of meprobamate. How was this incorporated into the results?

Sokoloff[77] reported that 400 mg. q.i.d. meprobamate and 30 mg. t.i.d. phenobarbital were both better than no sedation in controlling chronic pruritis ani or pruritis vulvae. Patients received x-ray and 1 per cent hydrocortisone ointment locally in all cases. Since much more drowsiness and interference with work efficiency was noted with the phenobarbital, the author concluded that meprobamate was the better drug for the purpose. Four points can be raised concerning this study. (1) It would have been much more satisfactory if the number of patients treated had been larger; 5 received phenobarbital, 14 received meprobamate, and 10 were under no sedation. (2) Nothing is said about the way in which patients were assigned to the three widely different sized groups. No comparison among groups is legitimate unless this is done in an unbiased fashion (e.g., assigning patients to groups by lot). (3) No firm conclusion can be drawn regarding the efficacy of either of the "active" medications. A placebo group should have been used in place of the no treatment group. (4) The possibility of experimenter bias should have been minimized by arranging matters so that the physician remained unaware of which patient was in which group.

Eisenberg[78] reported that meprobamate helped in the management of anxiety associated with various allergic conditions (predominantly asthma, hay fever, eczema, and urticaria and angioneurotic edema). He gave 83 patients two 2-week courses of the drug with a period of similar length on mephenesin sandwiched between. The latter was used in lieu of a placebo. Thirty-two (38 per cent) showed improvement during the first period on meprobamate, 8 of 78 patients who took the mephenesin (10 per cent) improved on it, and 28 of 82 who took the second course of meprobamate (34 per cent) showed improvement. (Why the numbers undergoing each leg of the trial differ is not clear from the paper.) Interpretation of these findings is clouded since the physician was not "blind" as to when patients were on each drug. The author made the further error of reporting on the drugs as if they had been given to independent groups.

Occasionally an author will mention the administration of placebos, but be vague as to how and when they were given. Pennington[79] for example, in a study of premenstrual tension, mentions that each patient received placebo for at least one month. But what month? Also, apparently, the placebos were dispensed by the physician, who was aware of what was being given.

Lamphier[80] gave postoperative patients a dose of meprobamate that was usually 400 mg. t.i.d. for a length of time that cannot precisely be determined from the published paper. A "satisfactory therapeutic result" was shown by 176 of 184 such patients (96 per cent). No data on a placebo control group are reported, although such a group is casually mentioned in the summary.

Rushia[81] reported on the hypnotic properties of meprobamate in a situation where anxiety was thought to play a part. He compared it with secobarbital in patients scheduled for surgery the next day. He found that 24 of 33 patient (73 per cent) taking 800 mg. of meprobamate at 9:00 P.M. said that they had slept all night when questioned upon coming to the surgical suite the following morning. This compared with 15 out of 33 (45 per cent) on 100 mg. of secobar-

bital. Rushia also found that two 400 mg. doses of meprobamate, given at 6:00 P.M. and 9:00 P.M., did not lead to appreciably better results than the small dose of the barbiturate. The study is marred by a lack of adequate precautions to rule out experimenter bias: the physician apparently knew which drug the patient was on when interrogating him about his sleep. The same comment can be made about an uncontrolled study by Damia and Fantoni,[82] who say that 800 mg. of meprobamate in the evening and 400 mg. more the following morning gave patients scheduled for morning surgery a good night's sleep and rendered them less anxious.

Castrovilli, Ginoulhiac, and Merli[83] report an uncontrolled study that found meprobamate of use in reducing the anxiety of patients undergoing various anxiety-inducing diagnostic tests.

Kern[84] used meprobamate as preoperative sedation for office surgery on the eye, ear, nose, and throat. No quantitative data are reported in this completely uncontrolled study. The author merely states that "most" of his patients "became quiet, relaxed and cooperative within 20-30 minutes" of a dose that was usually 400 mg. for adults, 200 mg. for children.

Meprobamate has also been used to try to decrease the apprehension of disturbed patients awaiting electroshock therapy. West and daFonseca[25] report on 15 cases of endogenous depression where 400 mg. meprobamate was administered one hour before E.C.T. "No marked effect was noted in the allaying of apprehension in these patients nor in the shortening of the post-E.C.T. period of confusion." The study was reported only incidentally to another report. It was apparently uncontrolled.

Thal[85] gave 400 mg. to 120 patients one hour before they received shock. The resulting changes in their behavior, when compared with that of the patients who received no medication, were little short of astounding. Fifteen minutes prior to shock, the premedicated group is described as: "All lying relaxed, without apprehension, unconcerned with immediate surroundings; but wide awake; no drowsiness. Usually read or looked at magazines. All have soft facial expressions; little conversation, but may talk in soft voices; all respond with smiles to proper stimulus."

After the E.C.T.: "More alert. Obeyed direction to get up and go for coffee and sandwiches. Walked naturally to pile of slippers at door, selected their own, walked to bathroom, combed hair in normal manner; proceeded down hall in pairs or groups, talking and walking normally."

Contrasting strongly with this picture is that of the nonmedicated subjects. Before E.C.T. they are described thusly: "All more apprehensive; strained expressions; furrowed brows. Voices high pitched and loud. Most tried to sit up, and twisted sheets in agitation. Some tossed and turned, appearing uncomfortable."

After the shock treatment, this is how they appeared: "Longer reaction time. Arose and walked stiffly and hesitantly with strained expressions; had difficulty selecting proper slippers. In bathroom most did not comb hair; merely brushed hands through hair. Walked stiffly to food with strained faces, and very little conversation."

It is unfortunate that these results cannot be accepted at face value. The lack of a placebo group makes it quite impossible to rule out both the physician's and patients' biases. The groups are also not comparable for another reason. The experiment was carried out on a 40-bed open ward. Forty patients were run at a time. Patients choosing the 20 beds on the right received the premedication; those choosing the remaining beds got nothing. Patients were used in the study an unstated number of times. The author states that "Those who selected beds on the right side of the room for some treatments chose beds on the left side for others. Thus every patient received pre-electroshock medication throughout about half the course and also acted as her own control." No data are presented on this crucial point. It is apparent that this method of allocation of patients to treatments is about as far from an adequate randomization procedure as it is possible to get.

OL.
7
958

ALCOHOLICS

Turvey[86] includes in his study a report on 51 patients who had already completed 12 to 14 days of hospital treatment for acute alcoholism and who had been sent home. Of these, 48 reported subjective relief of nervous tension on a questionnaire. No controls were used. All of these patients had had other medications previously and were therefore "qualified to judge the sedative effects of meprobamate in the light of earlier experiences." How the questions were phrased is not stated, although it is well known that this is critical in interpreting the results. Furthermore, some patients (the number is not given) said that they were not as relaxed as after a barbiturate.

Proctor[87] confounded the effects of psychotherapy with those of meprobamate in his study of outpatient alcoholics. He reports that 30 of his 80 patients remained sober for 12 months under this regimen. No controls of any kind were used.

Fox[88] recommends a combination of chlorpromazine and meprobamate in the treatment of alcohol withdrawal symptoms. She started out with large doses of chlorpromazine, which, although effective, produced undesirable side effects. She therefore decreased the dosage of chlorpromazine and added meprobamate, which, by itself, she did not find to be effective. One wonders what effect she would have obtained by merely decreasing the amount of chlorpromazine. Fox also says that a control group was constituted from digesting the history of previous admissions for 16 of the patients. Again, we must point out that this shows a lack of appreciation of the significance of control groups.

Thimann and Gauthier[89] also administered meprobamate to acute alcoholics, immediately after treatment with chloral hydrate, paraldehyde, or insulin and report good results, but it is difficult to know what their good results are due to in the absence of proper controls.

Three studies on the use of meprobamate for the anxieties of chronic alcoholics appear to have been well designed and executed.

Greenberg, Lester, Dora, Greenhouse, and Rosenfeld[90] studied meprobamate in both hospitalized alcoholics and ambulatory chronic outpatient alcoholics. In their study of the latter they gave 400 mg. q.i.d. for 3 weeks to half of 67 patients, placebos to the rest. Patients were seen by a therapist weekly and were rated on a variety of common symptoms. The therapist was not told which

group a patient was in. Comparison was made between admission status and status at the end of treatment. Analyzable data were gathered on eight symptoms. The drug produced a significant improvement in 6 of them: psychomotor agitation, anxiety, irritability, insomnia, depression, and demand for medication. Craving and anorexia were not affected significantly. The differences between percentages helped by drug and placebo were marked, 88 per cent on drug versus 33 per cent on placebo for anxiety being the largest.

In their second study they gave 50 of 100 "patients exhibiting the most acute and pronounced phases of psychomotor agitation, anxiety, irritability, nervousness, apprehension and other symptoms of hangover that, in general, were the reason for this hospitalization" a mean of 2.4 Gm. meprobamate daily for 1 to 2 weeks. The other 50 received placebos. Again the experimenters making the evaluation of improvement were blind as to what patient was receiving what drug. But here, of the symptoms rated—the list discussed above was again used—only insomnia proved to be helped significantly by the drug. A global judgment of "general improvement" was also made by the therapist at the end of treatment and proved significantly different for the two groups: 64 per cent for drug, 10 per cent for placebo.

Smith, Rutherford, and Fanning[91] compared meprobamate 400 mg. t.i.d. to phenaglycodol (Ultran) 300 mg. t.i.d. and placebo in chronic male alcoholics committed to a state mental hospital. Of 32 patients started on the study, 26 finished 2-week periods on each treatment. Patients were interviewed weekly by a research nurse who was unaware of the medication being given at the time of the interview. No differential effects of the drugs were observed. This otherwise well-designed study was marred only by a lack of some sort of counterbalancing to rule out possible order effects: all patients received phenaglycodol first, placebo second, and meprobamate third.

COMPARISONS WITH STANDARD DRUGS

We have been addressing the question of the relative efficacy of meprobamate and placebo. A separate and perhaps more important one from the standpoint of clinical medicine is this: how does meprobamate compare with other pharmacologic treatments for anxiety?

While several authors mention comparisons between meprobamate and standard medications, only two of the studies appear to have been adequately controlled. One was by Raymond and associates,[35] discussed previously, which showed that a daily dose of amobarbital 300 mg. performed better than a daily dose of meprobamate 2,400 mg. on neurotic outpatients. The other was done by West and daFonseca.[25] They compared meprobamate with amobarbital in 51 neurotic patients. Tablets of either 400 mg. meprobamate or 65 mg. amobarbital were given three times a day with an additional one or two tablets at night. Courses on the two drugs were alternated each clinic visit with half the patients starting on each. The length of time a patient remained on a particular drug before being switched is not specified further. No difference in efficacy was noted. Thirteen received more benefit from the barbiturate; 13 received more benefit from meprobamate. Sixteen got no benefit from either drug, while 9 got equal benefit from both.

There is then, at this time, no evidence that meprobamate, even if it were granted that it is useful for treating anxiety, performs better than the barbiturates. Moreover, there is no satisfactory evidence that, on the basis of side effects, it is a more benign compound than the barbiturates in its addiction liability and hypnotic properties. In a well-designed study performed on chronic schizophrenics, Ewing and Haizlip[92] showed that daily doses of 3,200 or 6,400 mg. for 40 days led, upon cessation of active drug, to withdrawal symptoms in 44 out of 47 patients. The symptoms closely mimicked those usually observed with barbiturate addiction. They also observed the development of tolerance, another index of addiction properties. Tucker and Wilensky[56] observed convulsions and anxiety upon withdrawal. Gorfinkel and Kline also reported abstinence convulsions in their uncontrolled trial (see Barsa and Kline[50]). Others, including Borrus,[7] reported drowsiness the first few days, then its disappearance; that is, the development of tolerance.

VOL.
7
1958

Stough[93] studied the possible addicting properties of meprobamate by subjecting prisoners to two kinds of treatment schedules. In one, the drug was discontinued abruptly (with placebo substituted); in the second, the dosage was gradually reduced. Abrupt cessation of the drug led to a sudden resurgence of previous neurotic symptoms and headache, insomnia, and restlessness. Two of 49 subjects had grand mal seizures. When the drug was discontinued by stages, these symptoms did not appear. Stough also reports the development of tolerance. These results are evidence in favor of the hypothesis that meprobamate possesses some addiction liability.

The fact that meprobamate may help in the management of alcoholism (Greenberg and associates[90]) indicates that it may be partially equivalent to alcohol in its physiologic effects. This is true of the barbiturates (Fraser, Wikler, Isbell, and Johnson[94]) and one might suspect that it would be true of any agent which is effective against the alcohol abstinence syndrome. In this connection, ten of the 13 patients discovered by Lemere[95] to have indulged in excessive self-medication with meprobamate were alcoholics who were abstemious at the time. Lemere also reports that the symptoms of excessive intake are indistinguishable from alcohol intoxication, a finding that has often been reported for the barbiturates (Fraser and associates[94]). Lemere's observations, however, were not obtained in a manner that guaranteed freedom from bias.

While the early studies of meprobamate described it as devoid of hypnotic effects, many of the papers reviewed here mention sleepy and groggy patients. Trustworthy data on this point are scarce. The only controlled trial of meprobamate as a hypnotic was conducted by Lasagna,[96] who found 400 to 800 mg. to be equivalent to 100 to 200 mg. of phenobarbital. Rushia[81] also found it to be a fair hypnotic, but in a study that was only partially controlled. Naturally, a hypnotic given in the daytime will have sedative effects. A useful and perhaps financially rewarding (to patients) study would be to explore thoroughly the "tranquilizing" potency of the barbiturates, varying dose, and dose level over a wide range.

CONCLUSIONS

We believe we can make the following generalizations on the basis of the literature reviewed.

1. *There is no good evidence that meprobamate can be distinguished from a placebo in treating anxiety in psychiatric outpatients.* Only the studies by Folkson,[26] Koteen,[34] Raymond and associates,[35] and one of those by West and daFonseca[25] provided the controls required for such a comparison. The raw data of the last named may well contain evidence of a difference in favor of the drug. We have discussed the reasons why we cannot accept the statistical analysis upon which West and daFonseca based their conclusion. Koteen's study, although it suffers from the same error in analysis, was accepted as showing no difference between drug and placebo because he provided enough raw data to check and affirm his conclusion. The Raymond and associates and the Folkson studies were quite unable to differentiate between drug and placebo.

2. *There is evidence that meprobamate is better than a placebo in treating anxiety in hospitalized neurotic and psychotic patients.* Here there are five well-controlled studies. Three yielded statistically significant positive results: Heller, Walton, and Black[54] with neurotics, Tucker and Wilensky[56] with psychotics and Jensen, Kristjansen, and Paerregaard[55] with senile patients. The small study on neurotics by the last named authors was negative, but the differences were in the same direction. The Hollister, Stannard, and Drake[53] study of a small number of psychotic patients also missed statistical significance, but it is suggestive of the same effect established more firmly by Tucker and Wilensky.

We should point out the possibility that the drug's seemingly differential effectiveness in our various patient groups may be contaminated by other factors. For instance, most of Tucker and Wilensky's psychotic patients, who were helped more by meprobamate than by placebo, were taking 1,200 mg. q.i.d. in the last weeks of the study. This is far larger than any dosage used in the controlled studies of outpatients. It is also apparent that the hospitalized patients are more likely to have actually ingested their pills than the outpatients.

3. *No good evidence is available demonstrating a difference between meprobamate and a placebo in the management of anxiety accompanying physical complaints or induced by a therapeutic or diagnostic procedure.* There is no satisfactory study on either point.

4. *There is evidence that meprobamate is better than a placebo in the treatment of outpatient alcoholics and some evidence for its efficacy in acute alcoholism; there is no evidence that it is useful in managing chronic hospitalized abstinent alcoholics.* The first statements refer to the Greenberg and associates studies[90]; the last to Smith, Rutherford, and Fanning.[91]

5. *There is no good evidence that meprobamate is any better than a barbiturate in assuaging anxiety. There is some evidence that it may not be as good.* We refer here to studies by West and daFonseca[25] and Raymond and associates.[35]

It is important that the reader understand what we are and what we are not saying. We are not saying that meprobamate is not useful in the management of anxiety in outpatients or of anxiety associated with physical complaints. Similarly, we are not saying that meprobamate is no different from the barbiturates. What we do wish to say is that no reliable evidence exists that it fulfills the claims made for it in these respects. It should be evident that totally uncontrolled studies of the effects of a new drug, especially when the dependent

variable is something as amorphous and elusive as anxiety, can be misleading. A striking testimonial to the validity of this statement is the way in which the popularity of new drugs typically runs through the well-documented cycle of panacea, poison, pedestrian remedy.

The high incidence of uncontrolled studies is not a feature confined to drugs affecting behavior. It seems characteristic of clinical research, as was amply shown by Ross[97] in his review. When one considers that the principles of the controlled experiment were written about by Bacon, in 1620, and Pascal, in 1648, (Boring[98]), an examination of this literature in 1958 can be somewhat discouraging.

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VOL. 7 195

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Book Reviews

VOL
7
195

ATOMIC ENERGY IN MEDICINE. By K. E. Halnan, M.D., D.M.R.T. New York, 1957, Philosophical Library, Inc. Pp. 157, indexed. Price $6.00.

In this small volume the author attempts to cover most of the applications of atomic energy in medicine. After an introductory chapter on elementary atomic physics, the uses of radioactive isotopes in research, diagnosis, and therapy are covered at some length, and a final section is devoted to the problems of protection against ionizing radiations. It is understandable that most emphasis is placed on the treatment of malignant diseases, but the author has interpreted his title broadly, including a discussion of x-ray therapy with both conventional and supervoltage ranges which some may consider out of place in such a volume. Be that as it may, the presentation is made in language which will be readily understood by those without much knowledge of medicine or of physics, and when technical terms have been used they are supplemented by clear and elementary definitions.

Most of the references are to work in Great Britain, and names which may be unfamiliar to American readers are frequently quoted, but this only emphasizes the great contributions made by that country to the original concepts of nuclear physics. On the other hand, the development of these ideas, especially in the field of high energy particle accelerations, by workers in the United States is freely acknowledged.

In his Foreword, the author emphasizes that readers of his book should not conclude that the treatments described are necessarily suitable for all patients. It is, therefore, unfortunate that he makes some dogmatic statements which are open to disagreement. For instance, he states that polycythemia is the one disease for which radioactive isotopes are the *only* effective treatment, where substitution of the word *most* for *only* would be more accurate. Again, radiophosphorus is said to be the most satisfactory isotope for brain tumor localization although compounds containing radioiodine are more commonly used and are more convenient in that counting may be made over the intact skull. No criticism can be leveled at the absence of mention of the newest developments of isotopes in diagnosis and therapy; in fact, the book is notable for the inclusion of much experimental work of recent interest.

The production of the book is adequate, and no misprints as serious as that quoted by the author of "unclear physics" for "nuclear physics" were noted, but it seems a pity that the plates are all placed together at the beginning of the book. If this was for reasons of economy, it appears strange that the price of the book could not be reduced. Incidentally, it is doubtful if Plate 9, purporting to illustrate measurement of thyroid uptake, would be clear to any person unfamiliar with the technique; and the lesion illustrated in Plate 6 would seem to this reviewer to be unsuitable for telecobalt therapy.

These criticisms are mere quibbles, however, and this small volume can be highly recommended to anyone wishing to become more familiar with the multitude of developments of the discoveries of the Curies, Rutherford, Joliot, and others which have been made in medicine for the benefit of mankind.

Robert J. Dickson

NON-GROUP ENROLLMENT FOR HEALTH INSURANCE. By Sol Levine, Ph.D., Olin W. Anderson, Ph.D., and Gerald Gordon, Cambridge, Mass., 1958, Harvard University Press. Pp. 171. Price $5.00.

The authors present the results of a survey conducted by them for the Health Information Foundation of New York City, designed to assist voluntary plans and private insurance organizations to increase enrollment and benefits of the people who do not have a common employer.

The report describes an intensive, objective study of five Blue Cross plans that have experienced varying degrees of success in meeting the problem of non-group health insurance coverage by application of accepted administrative techniques for approaching inclusive enrollment of the uncovered elements of the population. The study is unique and adequately documented for the statistically minded. The narrative considers the current problems of extending enrollment, the magnitude of non-group coverage, the future of non-group enrollment, and the research possibilities in this field. The basic philosophy of the Blue Cross movement which has been the traditional guide for most of the plans is described in a statement of principles derived during the study.

The report commends itself to those concerned with the problems of the costs of hospital care and who envision the solution as within the scope of voluntary prepayment.

Harry L. Chant

OL.
7
958

PHYSICAL METHODS IN PHYSIOLOGY. By W. T. Catton, M.Sc., New York, 1957, Philosophical Library, Inc. Pp. 375, indexed. Price $10.00.

Research workers in mammalian physiology have long needed a book which delved into the physical aspects deeply enough to put in perspective the striking quantitative advances of the last decade. Catton has done this for several of the major physiologic systems: blood, circulation, respiration, muscle, nerve, and body heat. He compares the methods, quantitative data, functional relationships deduced, and physical laws applied in these six fields in a unified and readable way. The expository level resembles Physiological Reviews, but frankly by-passes much of the biochemistry in order to stress and unify the physical aspects.

This book develops the quantitative aspects of each method of measurement more deeply than can a textbook of medical physiology, handling the physical concepts and background concisely, but correctly, in the main. It could therefore provide an introduction for physicists as well as physiologists entering research. A biophysicist might have fitted less ably the physical aspects into the physiologic picture but would have treated more critically the details, errors, and interpretations of the existing methods and analyses. The index is unusually thorough, and the extra stress on British and Continental references is probably good for us here.

S. A. Talbot

PRACTICAL NURSING TODAY—Attitudes, Knowledge, Skills. By Margaret C. Esau, Barbara R. Fallon, Kathryn G. Frentzos, Elizabeth C. Phillips, and Eleanor A. Tourtillott, New York, 1957, G. P. Putnam's Sons. Indexed, pp. 525. Price $5.95.

Practical Nursing Today presents a splendid over-all picture of the attitudes, knowledge, and skills which are required of today's practical nurse. The introductory chapters clearly define the practical nurse as a member of the nursing team, her organizations and their functions, and the importance of accreditation and licensure. Miss Phillips' discussion of opportunities afforded the practical nurse is concise and clear-cut.

The discussion in Part Two of the "Normal Body," and in Part Three of "Today's Family," contains pertinent information for lay people, as well as the practical nurse, as it relates to body functions and normal habits which promote sound heath. The description of the family depicts wholesome living and clearly emphasizes the fact that each individual has an important role in the family unit.

The chapters dealing with treatment and nursing care of common illnesses are easy and interesting reading as well as informative and concise. Certain nursing measures such as mouth care and prevention of pressure sores could profitably be discussed in more definite detail. However, splendid supportive nursing care is emphasized throughout these chapters.

Many topics are elaborated upon in the last few chapters. There is emphasis throughout on the need for a pleasant, cheerful, and clean environment for the patient. The patient-centered discussion clearly points up legal implications for the worker and enumerates safety measures in relation to the patient and the worker herself. Especially practical is the treatment of the emergency or accident situation. The need for accuracy and honesty is emphasized. There is a tendency throughout the book to pin-point the importance of a clear understanding of nursing practices in relation to purpose and expected results.

Rachel Fee

YEAR BOOK OF CANCER. By Randolph Lee Clark, Jr., B.S., M.D., M.Sc. (Surgery), D.Sc. (Hon.), and Russell W. Cumley, B.A., M.A., Ph.D. Chicago, 1957, The Year Book Publishers, Inc. Pp. 572, with 210 figures; indexed. Price $7.50.

Neoplasia is a common phenomenon which is dealt with at various levels by clinicians and laboratory investigators alike. Their numerous observations are published in many journals and bear the imprint of several scientific disciplines.

The need for a volume containing abstracts of the significant "cancer literature" is obvious. The editors of this first *Year Book of Cancer* have attempted to fulfill this need by assembling a board of 119 physicians and medical scientists and charging them with the task of editing the abstracted material which fell within their area of greatest competence.

The format of this Year Book is quite similar to the others of this series. The contents of this particular volume deal mainly with the clinical manifestations and therapy of neoplastic diseases but included also are abstracts of certain laboratory investigations which should further stimulate physicians and surgeons in their attempts to manage their cancer patients most intelligently.

The *Year Book of Cancer* appears to have succeeded in its stated purpose, and each annual edition should serve to increase the physician's capacity to discharge his clinical responsibilities more effectively.

Albert H. Owens, Jr.

SELF-HELP DEVICES FOR REHABILITATION. Project conducted by New York University-Bellevue Medical Center, New York, N. Y., Dubuque, Iowa, 1958. William C. Brown Co. Pp. 418, illustrated. Price $4.75.

This loose-leaf volume is an attempt to illustrate all self-help devices and gadgets useful for all types of handicapped patients. Braces and prosthetic appliances are not included. The devices are presented in groups such as those used for self-care (dressing, toilet activities, eating, bed attachments), communication, travel, household equipment, house adjustments, and recreation. A second section illustrates devices used in therapeutic exercise.

The question will arise as to the completeness of this study. A thorough investigation of the literature, letters to hospitals, clinics, rehabilitation centers, and the United States Patent Office and a search of catalogues seems to have insured as complete coverage as is possible.

Each item is illustrated in use; its cost and vendor is designated, and its purpose outlined. The illustrations are large, clear, and well arranged.

The book should be of interest not only to those who specialize in treatment of the disabled, but to anyone who even occasionally sees a handicapped patient.

Douglas Carroll

PSYCHOTROPHIC DRUGS. Edited by S. Garattini and Z. Ghetti. Proceedings of the International Symposium on Psychotrophic Drugs, Milan, May 9-11, 1957. New York, 1957, Elsevier Publishing Company. Distributed by D. Van Nostrand Company, Inc. 606 pp., indexed. Price $19.50.

This expensive, gorgeously bound and printed volume is a strange mixture of superb and third-rate stuff. Many of the workers prominent in the field of psychopharmacology attended the Symposium, and their contributions are, by and large, informative and provocative. Other, less famous, scientists were also on hand, and in many cases present their own specific approaches, theories, or data clearly and completely. Still others (primarily clinicians), who might be more amply described as "notorious" than "well-known," were unfortunately also invited and served only to clutter up the proceedings with uncritical remarks and data, detracting considerably from the excellence of the book.

My own favorite papers were those by Rothlin (on LSD and related drugs), Weiskrantz (on reserpine and behavioral nonreactivity), Miller (on motivational studies in animals), Burns (on the electrophysiologic basis of cerebral function), and Plummer, Sheppard, and Schulert (on reserpine metabolism).

Despite its faults, this book could be read with profit by anyone interested in modern psychopharmacology. For those who cannot read the relatively few reports in French, Italian, or German, English summaries are available in the text.

Louis Lasagna

VOL.
7
1958

CLINICAL TOXICOLOGY. The Clinical Diagnosis and Treatment of Poisoning. By S. Locket, M.B., B.S., M.R.C.P., (London), St. Louis, 1957, The C. V. Mosby Co. 772 pp., indexed. Price $20.00.

There are few fields that need good comprehensive compendia more than the field of toxicology. Most tests on toxicology suffer from excessive preoccupation with forensic problems or toxicologic methods, and from being written by people without clinical experience in the handling of poisoned patients. With Dr. Locket's book, the medical profession has a comprehensive treatise with primary emphasis on treatment. Locket is obviously bright, critical, and experienced, and he has given us the best toxicology book available for the practicing doctor. The book has its faults: it is not always well organized, it at times detours into irrelevant material, and it is occasionally incomplete or in error. One hopes that future editions will remedy these faults.

There is a superb chapter on gastric lavage which ought to be read at least once by every physician, and there are two useful sections by specialists on the identification of poisons and poisonous plants. Despite its substantial cost, this book would be a good buy for any doctor's office.

Louis Lasagna

Announcements

AVAILABILITY OF RESULTS OF RESEARCH AND DEVELOPMENT IN THE U.S.S.R. AND OTHER SOVIET ORBIT COUNTRIES IN THE FIELD OF SCIENCE, TECHNOLOGY, AND MEDICINE

Pergamon Institute, a nonprofit foundation, has recently been formed in Washington, D. C., and is in course of formation in London, for the purpose of making available to English-speaking scientists, doctors, and engineers (from all countries that are members of the United Nations), the results of scientific, technological, and medical research and development in the Soviet Union and other countries in the Soviet orbit.

The International Council of Scientific Unions, during the recent meeting of its Executive Board in Brussels, decided to include a token subvention to the Pergamon Institute in the allocations for 1958, in recognition of the value to international scientific activity of the Aims and Purpose of the Pergamon Institute. Over a hundred scientists of international standing from many countries have given their support and will supervise the affairs of the Institute.

The formation and purpose of the Institute was much influenced by a report to the United Kingdom Government by its Advisory Council on Scientific Policy, under the Chairmanship of Sir Alexander Todd, F.R.S., which among other things analyzed the position as follows:

". . . There would, of course, be no problem if Russian were widely read, but our information is that only about 2 per cent of our working scientists can read Russian, compared with 80 to 90 per cent who read French and 60 per cent German. The first thing to be done, therefore, is to encourage the teaching of Russian as an important modern language in schools and universities. . . ." Authoritative sources in the United States also agree that less than 2 per cent of the working scientists in America can read Russian.

Allan T. Waterman, Director of the National Science Foundation in his recent report to President Eisenhower "Basic Research—A National Resource" said that "recently several American industrial laboratories spent five years and at least $200,000 conducting studies of the design of electrical circuits only to find afterwards that the work had already been done. It was described in a Russian article published in a Soviet journal before the studies started."

He went on to say, "From published Russian sources, it appears that some 24,000 scientists, or about 14 per cent of Soviet scientific manpower, devote their time to basic research. This figure is probably somewhat higher, say between one-fifth and one-third, than the number of scientists—on a full-time equivalent basis—engaged in basic research in the United States. The Soviet Union spent more than 11.6 billion roubles on research and development in 1955, somewhat in excess of 1 per cent of its gross national product, and the proportion that went to basic research is unknown. However, the proportion is presumably less than that based on manpower estimates. These and other facts suggest the following picture: (1) a remarkably high rate of industrial and technological growth, as indicated by the high rate of increase in gross national product; (2) an even greater relative increase in research and development as indicated by the increasing ratio of research and development to gross national product; (3) a country still technologically underdeveloped, as indicated by the low starting level of its research and development—and the low level which still prevails—relative to the United States; and (4) a relatively heavy emphasis on basic research certainly heavy if compared with the United States, but differing from our situation in the authoritarian controls exercised in a dictatorship."

VOL
7
195

As a result of recently announced scientific and technological developments in the U.S.S.R. there is a great need, as well as pressure, from scientists, universities, government departments and industrial firms, to overcome the language barrier and to make available rapidly in English the significant results of research and development in the U.S.S.R. in the fields of science, technology, and medicine.

It is one of the primary tasks of the Pergamon Institute to fill this need quickly by the initiation of large-scale translation programs of complete journals and books, as well as individual papers, in all the critical fields of science, technology, and medicine.

The following are the projects which have already been started or are being planned by the Institute in association with and with the financial assistance of various Government departments, learned societies, and private organizations, and some of the services which are available:

1. It is planned to hold a Symposium during the summer of 1958, either in Washington or London, sponsored by the Institute and several interested Universities, to examine the following problems: (a) how to assist with the establishment of extracurricular courses for the teaching of Russian in the science, medical, and engineering faculties at higher seats of learning in the English-speaking world; (b) how to teach the reading of Russian scientific and technical texts to scientists and technologists in the minimum amount of time; (c) what tools of learning are required.

2. Discussions are taking place with the relevant authorities in the U.S.S.R. on the commissioning of a series of review volumes, with complete bibliographies, covering broad areas of Russian scientific, medical, and technical progress for the period 1920-1956.

Journals Being Translated by the Institute and Now Available in an English Edition.—

3. The Institute now publishes a number of selected Russian journals in translation: Atomnaya Energiya (Atomic Energy), Problems of Virology,* Problems of Hematology and Blood Transfusion,* Journal of Microbiology, Epidemiology and Immunobiology,* Biophysics,* Problems of Oncology,* The Sechenov Physiological Journal of the U.S.S.R.,* Elektrichestvo (Electricity), Physics of Metals and Metallography,† Abstracts of U.S.S.R. Metallurgy,† Bulletin of the Academy of Sciences—Geophysical Series,‡ Abstracts of Geophysics—U.S.S.R. Eastern Europe and China,‡ Radio Engineering,§ Radio Engineering and Electronics,§ Telecommunications,§ Applied Mathematics and Mechanics.§

Translation Program of Important Russian Books.—

4. The Institute is also assisting with the translation and publication of important Russian books on science, technology, and medicine; and several works will soon be available in English, including the work of Academician N. Semenov, who recently shared the Nobel Award for Chemistry with Sir Cyril Hinshelwood, and the classic course of Theoretical Physics by Academician Landau and his colleague, Professor Lifshitz. Academicians Semenov and Landau and Professor Lifshitz are cooperating with the institute in bringing their books up to date, by adding a great deal of new and hitherto unpublished research results. It is noteworthy that other Soviet authors, whose monographs, books, and articles are being translated by the Institute are also cooperating by bringing their work up to date, checking proofs, making available illustrations, etc. This cooperation is most valuable for the work of the Institute.

Institute Services.—Available to learned societies, Government departments, trade associations, individual scientists, doctors, and engineers.

1. Any person in the above categories wishing to keep informed of what is being published in the U.S.S.R. and other countries in the Soviet orbit may apply to the Institute to receive, free of charge, a monthly contents list in English of all the significant articles and books being currently published in his field of interest in these countries. Persons interested in any article men-

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*On the initiative and with the financial assistance of the National Institute of Health, United States Department of Health.

†With the financial assistance of the National Science Foundation and the Board of Governors of Acta Metallurgica.

‡With the financial assistance of the National Science Foundation and the American Geophysical Union.

§With the financial assistance of the National Science Foundation and in association with the Massachusetts Institute of Technology.

VOL.
7
1958

tioned in these contents lists may order from the Institute a full English translation which will be supplied with a minimum of delay. The charge for such a translation will be on a cooperative cost-sharing basis. This means that the costs will be shared equally with others requesting the article. The costs will be assessed on orders obtained for this translation over a period of 6 months, and the charges to recipients of these papers will be made 6 months after the first request.

2. The Institute will undertake to supply, on request, detailed and exhaustive bibliographical information on work published in the U.S.S.R. and other Soviet orbit countries on all subjects in the field of science, technology, and medicine; such services will be quoted for and charged at cost.

3. The Institute, with the assistance of its scientific staff, will undertake, on request, critical evaluation and selection of any work published in the field of science, technology, and medicine in the U.S.S.R. and other Soviet orbit countries. The Institute will also provide abstracts and résumés of such publications.

4. The Institute will provide, with the cooperation of the respective National Academies of Sciences of the U.S.S.R. and other Soviet orbit countries, to learned Societies, Government departments, and industrial organizations, books and journals published in the U.S.S.R. and the Soviet orbit countries, including microcards and microfilms, when available, of books and articles published over the past 20 years in these countries, including material published during the 1939-1945 war as far as available.

5. The Institute will undertake the additional translation of selected journals and books if suitably recommended by learned societies, Government departments, or trade associations.

6. The Institute can undertake, with the aid of its expert panel of translators, resident all over the world, translation work in all branches of science, technology and medicine from and into any language, including Chinese and Japanese.

7. The Institute will make available to learned societies and individual scientists, doctors and engineers throughout the world reciprocal services on the same nonprofit basis in return for their cooperation.

Qualified Translators Urgently Needed.—The Institute is urgently in need of qualified scientists, technologists, and doctors with a knowledge of the Russian language who would be able and willing to undertake translation work on a spare-time basis for which they would be remunerated.

Financial Support and Other Assistance Needed.—Nonprofit foundations, industrial corporations, Government departments, learned societies, and individual scientists desiring to assist in any way with this important program should write to the Administrative Secretary of the Institute outlining their ideas and suggestions.

For the first time in the United States, the World Health Organization, with delegations from 88 member countries, is holding its annual World Health Assembly May 26-June 14 in Minneapolis.

The delegates will come in contact with American health and medical leaders and will see a condensed sampling of health programs and research in this country through the post-assembly technical tours, which begin immediately following adjournment of assembly sessions. These tours were arranged by the United States Public Health Service, the Department of State, and W.H.O., assisted by the National Citizens Committee.

The American Hospital Association, the American Medical Association, the American Dental Association, and other organizations are sponsoring a reception on the evening of June 15. On the following day the topics of heart disease, mental health, nutrition, rehabilitation, cancer, tuberculosis, poliomyelitis, and radiation and health are scheduled for discussion in seminars.

Dr. Charles Mayo is Chairman of the over-all Arrangements Committee as well as Chairman of the Minnesota Committee, which was appointed by Governor Freeman. Dr. Ernest L. Stebbins of the Johns Hopkins Hospital is Chairman of the Technical Tours Program Committee.

OL.
7
958